About the Medical Research Scholars Program

This publication lists the 2015-2016 Scholars of the National Institutes of Health’s (NIH) Medical Research Scholars Program (MRSP), and outlines their research studies in their year-long participation in the program.

MRSP builds on decades of experience at NIH in training clinician-scientists, and provides outstanding U.S. medical, dental and veterinary students with advanced training in laboratory, clinical and translational research. Its one-year intensive training program enables the most promising clinicians to understand the biological underpinnings of disease and translate basic science into health care interventions.

Launched by NIH in 2012, MRSP combines and re-envisions two highly successful NIH training initiatives: the Clinical Research Training Program (CRTP) that operated from 1997 to 2012 and the HHMI-NIH Research Scholars Program that operated from 1985 to 2012. The program is designed for students who have completed their initial clinical rotations and are primarily between their third and fourth years of professional school. In the course of their year at NIH, MRSP Scholars work with an Advisor who provides research support and career guidance, and a Mentor, who helps them to develop a year-long laboratory, clinical or translational research project that aligns with their clinical interests and career goals. Based on the nature of their project, they conduct their research at one of the 27 Institutes or Centers within the NIH intramural program.

MRSP is distinguished from other training programs by the Scholars’ unique access to the full range of NIH resources. These include laboratories and clinical research facilities that are among the most extensive and highly regarded in the world; access to the NIH’s 27 intramural Institutes and Centers; NIH lectures and tutorials on seminal research and new clinical discoveries; and teaching rounds at the NIH Clinical Center, America’s Research Hospital. Scholars spend the majority of their time on their research but they participate in a complementary program of professional development, enrichment, scholarship and leadership opportunities.

Recognizing that successful biomedical research depends on the talent and dedication of the scientific workforce, NIH supports innovative training programs like MRSP that foster scientific creativity and exploration. NIH’s goal is to strengthen our nation’s research capacity, broaden our research base and inspire a passion for science in current and future generations of researchers.

For more information about MRSP or to learn about opportunities to support the program, please contact the Development Office at Development@fnih.org.
Psoriasis is a chronic inflammatory skin disease associated with increased aortic vascular inflammation, measured by 18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), and an increased risk of myocardial infarction. Patients with psoriasis are also more likely to suffer from comorbid depression and anxiety. Whether these comorbidities accelerate the development of subclinical atherosclerosis in psoriasis is unknown. The Mehta Lab studies psoriasis as a human clinical model of accelerated atherosclerosis. Within our longitudinal prospectively-enrolled cohort of patients with psoriasis we selected those patients who reported a history of depression (n=36) on survey, as defined by the use of medication or receipt of counseling, and matched them by age and gender to patients from the cohort who reported no history of psychiatric illness (n=36). In unadjusted analyses, vascular inflammation and coronary plaque burden were significantly increased in patients with self-reported comorbid depression as compared to patients with psoriasis alone. After adjustment for Framingham Risk Score, vascular inflammation ($\beta=0.23$, $p=0.026$), total coronary plaque burden ($\beta=0.14$, $p=0.047$), and non-calcified coronary plaque burden ($\beta=0.14$, $p=0.046$) were associated with self-reported depression. Self-reported depression in psoriasis is associated with increased vascular inflammation and coronary plaque burden, suggesting that psychiatric comorbidities may play an important role in promoting subclinical atherosclerosis beyond traditional cardiovascular risk factors in psoriasis.
Tumor associated macrophages (TAMs) and immature cells of the myeloid lineage are abundant in the pancreatic tumor microenvironment, govern clinical outcomes, and confer resistance to chemotherapy. Thus, this immune subpopulation offers opportunities for novel immune approaches against this deadly disease. RP-182 is synthetic 10-mer peptide derived from antimicrobial peptides within the early innate immune system that has demonstrated impressive effects in several inflammatory models. In silico modeling identifies binding with the CD206 cell surface receptor, a marker present on immunosuppressive TAMs and myeloid derived suppressor cells (MDSCs).

We sought to determine if RP-182 prolongs survival in an immunocompetent mouse model of pancreatic cancer and to clarify the mechanism of action of RP-182.

We hypothesized that RP-182 extends survival in immunocompetent mice and that this effect is mediated by the depletion of immunosuppressive CD206+ TAMs or MDSCs.

Treatment with RP-182/gemcitabine combination therapy prolongs survival in immunocompetent mice compared to gemcitabine alone (44 days vs 23 days, p<0.001). RP-182 treated tumors demonstrated downregulation of macrophage-associated genes and upregulation lymphocyte-associated genes. We found that RP-182/gemcitabine combination therapy decreases MDSC populations and tumor PD-L1 expression. While no effect on CD206+ TAMs was observed, MDSCs were decreased (>50%) in the combination group.

Based on these findings, we sought to determine if checkpoint blockade via PD-L1 antagonism might phenocopy the effect of RP-182/gemcitabine combination treatment. We found that α-PD-L1/gemcitabine combination treatment increased survival relative to gemcitabine alone.

Our results demonstrate that RP-182/gemcitabine combination therapy, but not RP-182 monotherapy, prolongs survival. This is in line with previous immune approaches, where gemcitabine-induced apoptosis increases presentation of tumor-associated antigens and reduces MDSCs. Our findings also suggest that downregulation of PD-L1, possibly mediated by MDSC depletion, might play a role in the mechanism of RP-182, making this strategy targeting several aspects of cancer-associated immune perturbations an attractive approach for further development.
Age-Related Macular Degeneration (AMD) is a major cause of blindness in the elderly worldwide, projected to affect hundreds of millions of people within the next few decades. As such, there is a continuing need to study interventions aimed at halting AMD progression. Unfortunately, AMD is difficult to study in clinical trials due to its slow progression and lack of good functional outcome measures. Visual acuity, conventionally used as a primary endpoint in ophthalmology, goes largely undisturbed until advanced disease and is thus an inadequate functional outcome measure for AMD.

Dark adaptation (DA), however, is one measure of visual function emerging as a potential biomarker of AMD progression with strong biological plausibility and increasing clinical evidence. One of several important natural history studies of DA is currently ongoing at the NEI. Cross-sectional results from this study at baseline showed that DA impairments are associated with AMD severity and presence of reticular pseudodrusen (RPD).

To further investigate the potential of DA as a functional outcome measure for AMD, we assessed longitudinal change in DA over two years and whether these changes were correlated with AMD severity. We found a small but statistically significant prolongation of DA among eyes with AMD as well as eyes with RPD, not observed in control eyes without disease. These changes occurred despite stable visual acuity over the follow-up period. Notably, RPD participants could only be followed using a modified DA protocol aimed at a different location on the retina thought to be less affected in terms of rod loss. Further study is needed to determine what mechanisms may be responsible for greater DA impairment in these eyes with RPD. We are optimistic that use of DA will become a valuable tool in future clinical studies of AMD; however, validation with large multi-center studies is warranted.
Resting state functional magnetic resonance imaging (RsfMRI) studies have shown disrupted cortico-cortical connections in individuals with Autism Spectrum Disorders (ASD). However, the pattern for younger autistic patients and the pattern of developmental change are much less clear. Some RsfMRI studies have shown aberrant age-related connectivity between sub-cortical regions, such as the striatum, and anterior aspects of the cerebellum and posterior temporal regions. Another study showed hyper-connectivity in children with ASD compared to age-matched typically developing children (TD). However, these studies utilized traditional seed-based correlation and/or independent component analysis (ICA), which are either not data-driven or make strong assumptions about the spatial and statistical nature of the underlying data. In this study, we utilized two novel whole brain resting state analysis methods to investigate the networks that are implicated in age-related functional connectivity changes in ASD using RsfMRI data from early adolescence to early adulthood (12 - 31 years of age). These novel methods, global connectedness method and whole brain seed-based search method, are both data-driven and free of assumptions about the statistical and spatial nature of the data. We found no age-related changes observed in ASD compared to TD. Moreover, ICA yielded the same null findings. These findings suggest that there might not be any age-dependent differences in adolescence and adulthood between ASD and TD individuals, at least as assessed by RsfMRI. A critical next step will be to investigate potential developmental changes in younger ages, such as in infants and children.
The number of individuals in the world above age 60 is expected to increase rapidly, and this aging pattern is especially significant in developing countries. The number of individuals diagnosed with chronic disease has grown due to this trend. Amyotrophic lateral sclerosis (ALS), the most common adult-onset motor neuron disease, is one such chronic disease. It is characterized by both upper and lower motor neuron degeneration and has a median survival of two to four years. Although ALS is relatively rare, the socioeconomic significance of the disease is extensive. It is therefore vital to project the epidemiologic trend of ALS. To date, there have been few published studies attempting to estimate the number and distribution of ALS cases in the coming years.

We performed a review of the current literature to identify incidence rates and median survival of patients with ALS. Using these data, we developed a code with use of R programming to estimate the number of individuals living with ALS in 2015 and 2040. Data were available for 10 countries and regions (China, Europe, Iran, Japan, Libya, New Zealand, Serbia, Taiwan, United States, and Uruguay). The number of ALS cases in these locations will grow from 80,162 in 2015 to 105,693 in 2040, representing an increase of more than 31%. The largest increase in cases will be seen in developing nations. Applying these figures to the broader world population, the estimated number of ALS cases is 186,398 in 2015 and 304,439 in 2040, representing an increase of 63% during this time period. We found that the number of ALS cases will increase by about 30% to 60% from 2015 to 2040. This projection fills a sizeable gap in the scientific literature, and understanding these trends is important to inform healthcare policy and more efficiently allocate local healthcare resources.
Inherited bone marrow failure syndromes (IBMFS) are a diverse set of genetic disorders characterized by the bone marrow’s inability to generate hematopoietic stem cells (HSCs). Allogeneic HSC transplantation and gene therapy offer potential cures but reduced numbers of matched donors and lack of gene-corrected autologous HSCs limit these treatment options. With the development of induced pluripotent stem cell (iPSC) technologies emerges the concept of generating iPSCs from an individual patient, correcting the defect using genespecific targeting for safe integration of the therapeutic transgenes (e.g. CRISPR/Cas9), and differentiating the disease-free iPSCs into transplantable HSCs. However, unlike their in vivo counterparts, human HSCs derived from iPSCs are incapable of efficiently reconstituting long-term hematopoiesis after transplantation in xenograft animal models, hampering full exploitation of the therapeutic potential of iPSC-derived cell products.

Here we successfully used an in vitro monolayer differentiation scheme to generate CD34+CD45+ Hematopoietic Stem/Progenitor Cells (HSPCs) from healthy donor-derived iPSCs for mouse engraftment studies. We further validated that these monolayer derived cells failed to engraft following NSG mouse transplantation. High throughput single-cell RNA sequencing (Drop-Seq) analysis was then used to compare single-cell transcriptomes of phenotypically-defined ex vivo-generated HSPCs to their matched primary donor-derived HSPCs. These investigations provided preliminary insight into the genetic programs that uniquely define both candidate populations. Through utilization of these techniques, we are better able to generate transplantable human HSCs with multi-lineage, long-term reconstitution potential for gene and cell therapies of inherited HSC disorders.
DNA methyltransferase 3A (DNMT3A) is a member of the DNA methyltransferase family primarily involved in de novo gene methylation. Mutations in DNMT3A have been associated with a wide range of hematological malignancies, most frequently acute myeloid leukemia (AML). Research suggests DNMT3A mutations produce a pre-leukemic state, rendering cells vulnerable to secondary oncogenic mutations and malignant transformation. This concept is supported by genome-sequencing data from over 10,000 healthy individuals in which the presence of clonal hematopoiesis driven by somatic mutations, most commonly DNMT3A, was associated with an increased risk of developing leukemia and all-cause mortality.

The mechanisms by which DNMT3A mutations contribute to malignant transformation have not been delineated, although a propensity of mutated cells to self-renewal has been postulated. The goals of this study were thus to determine the transcriptional and biological effects of DNMT3A knockout (KO) which contribute to leukemogenesis. To do this, we generated DNMT3A KO human cell lines using the novel gene-editing technology CRISPR/Cas9.

We successfully created four DNMT3A KO cell lines using K562 cells. In a growth curve analysis, we found that the DNMT3A KO cell lines exhibited significantly impaired growth compared to DNMT3A WT cells. Furthermore, we found that DNMT3A KO cells were significantly more susceptible to apoptosis and DNA damage after treatment with 5-FU. Finally, RNA-sequencing expression analysis revealed numerous differentially expressed genes and many dysregulated signaling pathways, including those of cell adhesion, apoptosis, and immune function.

We have shown that CRISPR-mediated DNMT3A KO in K562 cells can be used as a model to study the effects of DNMT3A mutation. Our data provide evidence that DNMT3A mutation alters K562 function in a global manner, consistent with its role as a DNA methyltransferase. Additional functional studies are required to elucidate the specific mechanisms by which DNMT3A mutation predisposes to leukemia.
Osteogenesis Imperfecta (OI) is a heritable bone dysplasia with increased susceptibility to fractures from minimal trauma. Growth deficiency is also a cardinal feature, with moderate to severe growth deficiency in most cases, and growth curves well below the 5th percentile for age. The majority of individuals with OI have structural defects in either of the genes encoding type I collagen (COL1A1 and COL1A2); types III and IV OI are the severe progressive deforming and the moderately severe types, respectively. There is a need for standardized growth curves for children with OI, to enable caregivers to know whether they are growing on the curves appropriate for their condition. Investigators also need to know whether OI growth patterns are influenced by the collagen chain in which the causative mutation occurs.

In this project, we used a database containing growth data (height, weight, head circumference) from age 2-16 years on 100 individuals with types III and IV OI, in order to assemble longitudinal growth curves. The data were compiled from 44 children with type III OI and 56 with type IV OI; of these, 56 had mutations in COL1A1 and 44 had mutations in COL1A2. Statistical methods involved merging of the full longitudinal curves to examine the impact of gender, type and mutation location. Gender and type were found to have significant effects on patient height, while mutation location did not. This was also true for patient weight curves. Neither gender nor type nor mutant chain affected cranial growth patterns. When data were subdivided by gender and type, it was apparent that the impact of OI type was significantly greater than the impact of gender. Finally, the longitudinal database was utilized to derive standardized growth curves by type and gender, using a statistical binning approach to obtain even contributions from all participants. Theses OI growth curves will be valuable to parents, caregivers and genetic specialists.
Hereditary spastic paraplegias (HSPs) are a group of genetically diverse neurodegenerative disorders resulting in spasticity and weakness of the lower extremities. The disease exhibits a prevalence of three to nine per 100,000 individuals. Over 70 gene products have been associated with HSP; these proteins are involved in a variety of roles including ER morphogenesis and microtubule-severing. Our lab investigates the functions of these proteins at the cellular level and within animal models to elucidate the pathogenesis of HSPs. The most commonly affected protein in HSP is spastin, a microtubule-severing protein that also performs other functions. To understand these roles, we studied two patients with mutations at the same spastin residue (499) who have different clinical manifestations. Patient one exhibits an arginine to cysteine (Arg499Cys) mutation, with a pure phenotype of spasticity and weakness. Patient two exhibits an arginine to histidine (Arg499His) mutation, with a complicated phenotype involving dysarthria and spastic quadriplegia. We sought to understand the cellular effects of these mutations and what specificities each mutation incurs. We obtained patient fibroblasts and analyzed levels of spastin and tubulin, which were decreased in mutants. We used immunofluorescence and specific assays to assess organelle structure and endosomal trafficking. Results suggest a delay in mitosis in mutant cells. Epidermal growth factor assays reveal an issue with endosomal trafficking in mutants, though transferrin assays indicate no issues with recycling. Organelle and cytoskeletal structure do not appear affected, while lipid droplet fusion stimulated by oleic acid seems decreased in mutants. These results, all of which were found to be more affected in the Arg499His mutation, suggest that the mutations result in early endosomal trafficking issues, delayed mitosis, and issues with lipid droplet metabolism. Given these findings studying endogenous spastin, the next step is to clone these mutations and overexpress the constructs to confirm these effects.
Patellofemoral pain (PFP) is one of the most common knee disorders in adolescent females. As just 5% of the literature on PFP focuses on the adolescent, there is a paucity of data examining the potential underlying etiologies for symptom onset in this population. The purpose of this study is to quantify if three-dimensional patellar maltracking is associated with PFP in the adolescent female and, if so, to investigate if patellar maltracking persists or resolves.

During 2008-2012, 13 female subjects (20 knees) with PFP and 12 healthy controls (20 knees) were recruited for this study. At the start of the study, all participants were between 12.0 and 15.7 years and had experienced menarche. For longitudinal evaluation, the cohort with PFP had a second visit at a mean of 4.5 years after the first (range, 3.5-4.9 years). During each visit, three-dimensional patellofemoral kinematics were captured during a dynamic knee extension maneuver using cine-phase contrast MR images.

Relative to the controls, the patellae in the cohort with PFP tracked laterally at all knee angles tested (p<0.001, p<0.001, and p=0.006 at 10°, 20°, and 30° of knee flexion, respectively). No differences were observed for the remaining kinematic variables. Between the initial and the four year follow-up visits, no differences were observed for any of the kinematic parameters. Both pain (p=0.012) and time spent per week on impact sports (p=0.025) decreased with maturation.

This is the first study to demonstrate that pathologic tracking patterns are present in female adolescents with PFP. As pathological patellar tracking in adolescents with PFP persists during skeletal maturation, maltracking likely plays a prominent role in the etiology and maintenance of pain. This may account for the chronic symptoms reported in recent studies. Although pain decreased with maturation, this appears to be at the expense of a reduction in sports participation.
Treatment of lymphoid malignancies with anti-CD20 monoclonal antibodies (mAbs) can be frustrated by the loss of cell surface CD20 through trogocytosis, creating “escape variants” that are no longer sensitive to the anti-CD20 mAb. In a clinical trial of treatment using the anti-CD20 mAb ofatumumab in chronic lymphocytic leukemia (CLL), we observed that patients with residual disease at the end of treatment frequently had these escape variants, but the variants carried the covalently bound complement activation fragments, C3d.

To test whether targeting C3d can eliminate escape variants after anti-CD20 therapy, we collected blood samples from CLL patients before (day 1) and 24 hours after administration of ofatumumab (day 2). A human IgG1 mouse chimeric mAb specific to C3d, developed in the lab, specifically bound and effectively killed CLL escape variants from day 2 through complement dependent cytotoxicity (CDC), NK cell mediated antibody dependent cellular cytotoxicity (ADCC), and phagocytosis. Importantly, non B lymphocytes were neither bound nor killed by the anti-C3d mAb, consistent with the highly targeted and selective deposition of C3d on CD20+ cells by ofatumumab.

Transfer of peripheral blood mononuclear cells obtained from CLL patients on day 2 of ofatumumab treatment into NSG mice and subsequent treatment with anti-C3d mAb led to significant reductions in tumor burden in both the peripheral blood and spleen compared to infusion of isotype control. In a second model, HBL2 cells, a CD20+ mantle cell lymphoma line, were xenografted into SCID mice. Mice were treated with either isotype, anti-CD20 mAb (ofatumumab or rituximab) or the combination of anti-CD20 and anti-C3d mAb. Addition of anti-C3d antibody extended time to tumor development and also prolonged survival significantly over CD20 targeting alone (median survival 34 days vs 79 days, p<0.0001). Targeting complement may represent a strategy that is universally combinable with other anti-tumor mAbs to circumvent the development of resistance through antigen escape.
Object: Chordoma is a low-grade malignant primary bone tumor most commonly affecting the axial skeleton and skull base. The intracranial location confers a high risk of complications to current management strategies including gross total resection and radiation therapy. LB100 is a novel small molecule protein phosphatase 2A (PP2A) inhibitor that has demonstrated preclinical efficacy against several solid tumors and has been shown to be safe in a recent Phase I clinical trial. We investigate the potential of LB100 as a radiosensitizing agent for chordoma.

Methods: We investigated the cytotoxic effects of radiation alone and in combination with LB100 on chordoma in vitro and in vivo. Cell cycle analysis and cellular DNA repair mechanisms were also evaluated.

Results: Treatment of cultured UCH-1 human chordoma cells with LB100 (4uM) augmented the cytotoxic effects of radiation therapy (RT) in vitro (dose range 0-16Gy). Furthermore, the ability of chordoma cells to repair double-stranded DNA breaks was limited with the addition of LB100 (number of foci/cell increased by a factor of 3.2). Compared to untreated controls, cultured cells exposed to combination therapy (4uM LB100 and 8Gy RT), exhibited a smaller percentage of cells in G0/1 phase (23% decrease). A concurrent rise in the percentage of cells in G2/M phase (21% increase) was also seen. Experiments with mice harboring subcutaneous UCH-1 chordoma xenografts are ongoing with an endpoint of reduction in cross sectional tumor area compared with controls.

Conclusions: These findings support a potential role for PP2A inhibition in combination with radiation therapy for treatment of chordoma. Decreased ability of tumor cells to recover from radiation-induced DNA damage is a possible explanation for the increased cytotoxicity. Moreover, the decrease in cells in G0/1 phase indicates reversal of cell cycle arrest while the increase in G2/M is consistent with enhanced radiosensitivity.
Human Papillomavirus (HPV) is the most common sexually transmitted disease, with clearance of infection seen in 90% of the general population within two years. Patients with primary immunodeficiency due to mutations in GATA Binding Protein 2 (GATA2), a transcription factor key to the development and maintenance of hematopoiesis, are susceptible to infections due to progressive monocytopenia and B and Natural Killer (NK) cell lymphopenia. Our purpose was to characterize the oncogenic nature of HPV disease in the GATA2 deficient cohort followed at the National Institutes of Health.

Sixty-eight GATA2-deficient patients were identified in a 15-year retrospective review of medical records. Evidence of HPV disease was found in 72% (n=49), with 40% (n=27) presenting with HPV disease as their initial manifestation of GATA2 deficiency. Of those with HPV-associated dysplasia (n=25), the majority had been diagnosed with severe dysplasia during their lifetime (n=21), with 10 patients carrying a diagnosis of oral or anogenital malignancy. 64% (n=16) had greater than two sites of dysplasia or malignancy. The management of HPV disease required surgery in 96% (n=24) of patients with dysplasia, and over half required greater than two surgical interventions (range 3 – 40 procedures).

In a comparison of GATA2-deficient patients with and without HPV disease, those with HPV had significantly lower monocyte (mean 20, range 0-7800) and NK (mean 9, range 0-230) cell counts/µL, p-values <0.0001 and 0.0002, vs patients without HPV, respectively. Mean CD4 T cell counts in the GATA2-deficient population were above 200 cells/µL.

Thirty of 34 GATA2-deficient patients undergoing bone marrow transplant had evidence of HPV disease, with 90% demonstrating resolved or stable HPV disease at a median of 1 year (range 0 to 10 years) after transplant.

GATA2 deficiency causes severe, multifocal HPV disease that improves with correction of the underlying defect. Future work will focus on identifying mechanisms of disease.
Due to its characteristically high genetic alteration rate, head and neck squamous cell carcinoma (HNSCC) represents an immunogenic tumor. The majority of HNSCCs display a T-cell inflamed phenotype, suggesting that patients with these tumors should respond to therapeutic approaches aimed at strengthening this tumor-directed immune response. A major barrier to the development of an effective anti-tumor immune response is the development of an immunosuppressive tumor microenvironment through expression of immune checkpoints such as programmed death ligand 1 (PD-L1) and recruitment of myeloid-derived suppressor cells (MDSCs).

IPI-145 (duvelisib) is an oral inhibitor of the p110δ/ϒ isoforms of phosphinositide 3-kinase (PI3K) that are differentially expressed in leukocytes. IPI-145 is currently under study in phase II/III trials for the treatment of hematologic malignancies, but has not been studied in solid tumors. We hypothesized that p110δ/ϒ inhibition could suppress solid tumor growth through functional inhibition of myeloid derived suppressor cells (MDSCs) within the tumor microenvironment of syngeneic murine oral cavity (MOC) tumor models of head and neck cancer.

Highly immunogenic MOC1 and poorly immunogenic MOC2 tumor-bearing mice were treated with daily oral doses of 15 mg/kg IPI-145 for 14 days and monitored for tumor progression. Following cessation of treatment, flow cytometry was used to study cellular immune correlates. Subsequent studies in the MOC1 model combined IPI-145 with anti-PD-L1 therapy.

Selective inhibition of p110δ/ϒ with IPI-145 resulted in a trend toward growth suppression of established MOC1 tumors, and had no effect on the growth of poorly immunogenic MOC2. IPI-145 increased infiltration and activation of CD8 T-lymphocytes and NK cells along with increased tumor cell expression of MHC class I and PD-L1 in MOC1 tumor bearing mice. Combined treatment with IPI-145 and anti-PD-L1 significantly decreased tumor size compared to anti-PD-L1 alone, demonstrating that IPI-145 can effectively sensitize immunogenic oral cavity tumors to anti-PD-L1 checkpoint inhibition.
Molecular mechanisms driving the development of head and neck squamous cell carcinoma (HNSCC) have recently begun to be discovered, with The Cancer Genome Atlas (TCGA) uncovering the genomic landscape of 279 cases of HNSCC. Alterations in cell death pathways were commonly found in the TCGA analysis, with approximately 30% of samples harboring amplifications of the gene encoding for Fas-associated death domain (FADD). Birinapant is a novel second mitochondria-derived activator of caspases (SMAC)-mimetic that targets and promotes degradation of inhibitor of apoptosis proteins (IAPs). IAPs prevent apoptosis by inhibiting FADD from interacting with its associated death receptors. Recent findings from our lab demonstrated synergistic activity of birinapant in combination with radiation in two murine xenograft models bearing tumor cells with endogenous FADD amplification. The goal of the present study was therefore to further characterize the role of FADD as a potential biomarker for predicting birinapant sensitivity. Additionally, we looked to assess the efficacy of birinapant in preclinical models of HPV(+) HNSCC.

We hypothesized that overexpression of FADD could modulate birinapant sensitivity in HNSCC. To test this, we transiently transfected a previously resistant HNSCC cell line with FADD vector and demonstrated subsequent sensitization to combination therapy with birinapant and TNFα. We then treated a panel of eight HPV(+) HNSCC cell lines with birinapant in combination with a death agonist; all cell lines reached half maximal inhibitory concentration (i.e. IC50) when treated with birinapant along with either TNFα or TRAIL. Finally, we tested birinapant in combination with radiation (which induces TNFα in vivo) in a xenograft murine model harboring non-FADD overexpressing HPV(+) tumor cells and found minimal treatment efficacy. Taken together, these results suggest that tumors harboring genomic alterations in FADD may be the most likely to respond to combination therapy with birinapant and radiation.
Leukocyte adhesion deficiency (LAD) type I is a genetic immunodeficiency characterized by loss of expression of CD18 integrin. We hypothesized that disruption of the CXCR4 chemokine receptor in human hematopoietic (CD34+) cells could lead to an engraftment advantage for such cells, and serve as a platform for treatment of patients with LAD type I using autologous hematopoietic progenitor/stem cells (HPCs). Our goal was to disrupt the CXCR4 locus while adding the corrected CD18 gene in human CD34+ HPCs, thereby correcting the LAD lesion while also giving the gene-corrected cells an engraftment advantage. We evaluated the efficacy of several methods of introducing the Cas9 endonuclease enzyme into human CD34+ cells in order to disrupt CXCR4. We found that non-integrating lentiviral vectors were able to transduce non-hematopoietic cells but were unable to transduce CD34+ HSCs, our ultimate target. We explored a high salt method to directly deliver the Cas9 protein; however, CD34+ cells were unable to survive long-term under conditions of high osmolarity. We then investigated a Cas9-KRAB-based silencing method which recruits protein methylation to induce inhibition. This resulted in some decrease in CXCR4 expression. Finally, we found that the most successful method of knocking down CXCR4 expression was by electroporating synthetic guide RNA (sgRNA) along with Cas9 protein into CD34+ cells.
The presence of myocardial fibrosis increases the myocardial extracellular volume (ECV). The expansion of the ECV has important prognostic implications and is related to adverse cardiac events. The amount of fibrosis in the heart is related to underlying heart damage, and early results indicate that this can be measured using cardiac magnetic resonance (CMR) imaging. However, CT (computed tomography) scanning of the heart is much more widely available and less expensive. The purpose of this study is to determine if CT methods can noninvasively determine the presence or absence of myocardial fibrosis, using CMR and histology as independent standards of reference.

A canine model of myocardial fibrosis was developed. Occlusion of the mid left arterial descending artery for 90 minutes was followed by reperfusion to induce myocardial infarction. Six to 10 weeks after surgery, animals underwent 3T CMR and cardiac CT imaging. Three dimensional (3D) CT ECV maps were created with an in-house software tool from pre- and post-contrast images. For CT ECV maps, infarct size was measured using a range of ECV thresholds (28-40%). Intraclass correlation coefficient (ICC) was calculated to evaluate scar volume agreement between MRI and CT.

The CT ECV cutoff for optimal CT and MRI scar volume agreement was determined under the given experimental conditions. The ICC was excellent. ECV maps showed improved contrast to noise ratio (CNR) vs. source 90kV images (11.4+/−2.7 and 5.37+/−2.3).

In a canine model, 3D CT ECV analysis with an optimized ECV threshold can accurately quantify myocardial infarct size with improved CNR over unprocessed CT images. ECV with dual energy CT showed excellent agreement with MRI findings, suggesting its potential in the assessment of focal fibrosis.
Cerebral palsy (CP) is a neuromotor disorder caused by an insult to the cortex of the developing infant in the neonatal or perinatal period. While the symptoms and disabilities of CP are primarily motor in nature, these children and adults can also suffer from multiple sensory, epileptic, or cognitive disabilities. One of the most common pathological gait patterns seen in this population is crouch gait, which is characterized by the increased flexion of the knee throughout the gait cycle. The purpose of our study was to review the historical and current treatments of crouch gait in the scientific literature. Current interventions and treatments are overwhelmingly surgical in nature and treatment guidelines rest on relatively low-level evidence from case series and uncontrolled cohort studies. Additionally, we investigated the effect of treadmill walking on the gait of these children, comparing kinematic, kinetic, and electromyographic measures between over-ground and treadmill walking in a set of patients with crouch gait. Initial data show multiple differences in important kinematic and kinetic gait parameters as these patients walk under the two different conditions. Another aspect of our research included the investigation of a novel powered knee ankle foot orthotic for the treatment and rehabilitation of crouch gait. This device provides extension torque to the knee at specified times throughout the gait cycle to correct the pathologic gait pattern during training, hopefully leading to improved gait mechanics during and after use. This research enhances the current understanding of the pathomechanics underlying CP crouch gait, and will hopefully aid in the future development of improved treatments and care for the CP crouch gait population.
The diagnosis of prostate cancer represents a unique challenge; the high incidence of disease is indelibly connected with over-diagnosis from PSA screening and trans-rectal ultrasound guided (TRUS) biopsy. Over-diagnosis leads to unnecessary morbidities from therapy. On the other hand, persistently high prostate-specific mortality suggests that many men with prostate cancer are not adequately diagnosed. Prostate multi-parametric MRI (mpMRI) guided biopsies have decreased the over-diagnosis of disease while increasing the diagnosis of clinically significant cancer. mpMRI is limited in wider application due to low inter-observer agreement and missed high-grade lesions. One approach to overcome this problem is through computer aided diagnosis (CAD) for mpMRI.

This project evaluated a novel CAD system in a first-reader study design. Nine different readers from 8 different institutions and 6 countries were recruited to evaluate 168 patients first on mpMRI alone and then mpMRI with CAD assistance. CAD was evaluated first and then readers could “rule-in” or “rule-out” disease by comparing to mpMRI. To facilitate this research, we developed a visual basic application that kept time and allowed validated-data entry and attachments of screen shots for easy correlation between readers. The data from this experiment has provided results for the feasibility of CAD in a first-reader study, the efficacy of PI-RADSv2 (a recently introduced scoring system for mpMRI), and pathways for improving radiologist’s performance on mpMRI.

Initial results indicate that the average sensitivity for all readers to detect index lesions (disease-driving lesions) was 78% for mpMRI and 86% for CAD (p=0.02), with index lesions sensitivity increasing 7.6% on average for each reader (p=0.02). Agreement on lesion detection increased from 56% for all readers with mpMRI to 73% on CAD (p<0.001). These results suggest CAD improves the detection of clinically significant disease and increases the agreement between readers of varying experience.
Moderate-to-vigorous physical activity (MVPA) is inversely correlated with cardiovascular disease (CVD). The importance of sedentary time (ST) in CVD development is currently under debate. Measuring PA and ST is difficult, but accelerometers noninvasively allow accurate, objective tracking throughout an entire day. Our objective was to determine the relationships between accelerometer-measured ST and MVPA, and CVD states.

This cross-sectional study utilized a random sample (N=643) of older adults from the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-RS). Participants wore an Actigraph GT3X accelerometer on the hip for one week. Information was collected on three states of CVD: metabolic syndrome, subclinical CVD, and clinical CVD. Adult Treatment Panel III guidelines determined metabolic syndrome. Subclinical CVD was determined by carotid plaques, carotid-femoral pulse wave velocity, and coronary artery calcium. Clinical CVD was determined using medical codes for stroke, myocardial infarction, or revascularization surgery.

Mean participant age was 80.2±4.8 years and the population was 38% male (n=247). The prevalence of metabolic syndrome, subclinical CVD, and CVD were 49%, 58%, and 31%, respectively. Participants were split into four quartiles based on minutes of ST per day [mean of least sedentary group 535±71 minutes/day; mean of most sedentary group 682±79 minutes/day]. Logistic regression was used with the least sedentary group as reference. Models were adjusted for age, wear time, sex, alcohol use, smoking status, education, and fatty diet.

The odds ratios (OR) were all above one and trended upwards with increasing ST quartile. The two highest ST quartiles showed OR for metabolic syndrome that were significantly different than one [2.04 (1.11-3.79) third quartile; 2.41 (1.23-4.8) fourth quartile]. When MVPA was added, this significance was attenuated. These results suggest that ST is not independent from MVPA in its relationship with metabolic syndrome. Lack of MVPA may be more important than ST in the development of metabolic syndrome.
2015-2016 Medical Research Scholars Program

Scholar: Michael J. Hochman  
School: Duke University School of Medicine  
Mentor: Richard Childs, M.D., RADM, USPHS, Senior Investigator, Laboratory of Transplantation Immunology, Hematology Branch; and Clinical Director, Division of Intramural Research, NHLBI  
Institute: National Heart, Lung, and Blood Institute (NHLBI)  
Research: Effect of Combining a Monoclonal Antibody Targeting CD123 with Natural Killer Cells Genetically Modified to Express High-Affinity CD16 on an In Vitro Model of Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is an aggressive cancer of immature myeloid cells that has a 25% five-year survival rate. Although 75% of patients who are treated with high-intensity induction therapy achieve complete remission (CR), half will relapse within two to three years. These data highlight a significant need for better therapies.

Clinical trials recently established that adoptive natural killer (NK) cell therapy can mediate regressions of hematologic malignancies. However, NK cells expanded ex vivo for adoptive transfusion shed CD16, attenuating their ability to mediate antibody-dependent cellular cytotoxicity (ADCC). Additionally, clinical data suggest that patients with B cell malignancies treated with rituximab respond better when they are homozygous for the high-affinity (HA) 158-V CD16 polymorphism (present in 10% of people) due to enhanced ADCC against antibody-treated targets.

The novel anti-CD123 monoclonal antibody, CSL362, targets chemoresistant leukemic stem cells that are responsible for disease relapse in patients who have achieved CR. Since AML patients could benefit from targeted antibody therapy combined with adoptive NK cell infusions, we investigated whether mRNA electroporation (EP) of expanded NK cells with HA-CD16 mRNA would enhance their capacity to mediate ADCC in vitro against CSL362-treated AML cells.

Human NK cells isolated from healthy-donor peripheral blood were expanded ex vivo for 12-16 days using irradiated feeder cells in media with interleukin-2 (IL-2). EP of NK cells was performed using the MaxCyte GT® Transfection System. Standard four-hour chromium-release assays were performed with a CD123-bright AML cell line, MOLM-14.

Baseline NK cytotoxicity against MOLM-14 was high (70%); adding CSL362 did not significantly increase NK cell killing of tumors. EP of NK cells reduced baseline AML killing, which increased with the addition of CSL362 but was inferior to non-electroporated NK cells. Other methods of genetic modification must be tested to explore further possibilities of augmenting NK-cell killing of CSL362-treated AML targets.
Tourette’s Syndrome (TS) is a common disorder characterized by verbal and motor tics. These tics may be a result of abnormally strong habit formation and altered learning. We sought to discover if subjects with TS required more trials to change their learned choices in a decision-making task with reward probability reversals. Six adult subjects with TS were recruited along with six healthy controls. Subjects performed a decision-making task with changing reward probabilities throughout the task. A machine learning algorithm was used to model reward expectation. Magnetoencephalography recordings were obtained during the task. Subjects with TS had a similar number of unrewarded choices in all probability blocks as compared to healthy controls, but with significantly increased midline frontal theta band power in the trials with high reward expectation. Source reconstruction of the signal showed the power change to originate from the mid-cingulate gyrus. Because reward expectation is encoded by dopaminergic neurons, this suggests altered functioning of dopamine in learning in Tourette’s Syndrome.
David J. Kirby
Johns Hopkins University School of Medicine
Marian F. Young, Ph.D., Senior Investigator, Chief, Molecular Biology of Bones and Teeth Section, Craniofacial and Skeletal Diseases Branch
National Institute of Dental and Craniofacial Research (NIDCR)
Understanding the Role of Biglycan in Fracture-associated Angiogenesis

Approximately 6 million new fractures occur each year in the U.S., with 5-10% of fractures complicated by non-union/delayed-union, or the failure/delay of bone to heal. The production of new blood vessels within the fracture callus, a process called angiogenesis, is essential for the fracture to heal. Impairment of fracture site vascularity has been identified as a major risk factor for non-union/delayed-union development.

Our lab has previously shown that the proteoglycan biglycan (bgn) plays a key role in the process of bone formation, but it was recently suggested to affect blood vessel formation within the fracture callus.

Our project goal was to determine if bgn has a role in fracture-associated angiogenesis, and attempt to identify the mechanism underlying this effect.

Micro-computed tomography angiography demonstrated mice deficient in bgn had significantly decreased vessel size and volume in the fracture callus at 7 days post-fracture compared to wild-type mice. Real-time RT-PCR confirmed decreased expression of PECAM-1, a marker for endothelial cells, in the fracture callus. Immunofluorescence and immunohistochemistry showed co-localized expression of bgn and endostatin, a potent inhibitor of angiogenesis, in the fracture callus. In an endothelial cell tubule formation assay, bgn was able to significantly inhibit the antiangiogenic effect of endostatin. RNA sequencing data revealed that bgn-deficient mice have differential expression of integrins important in angiogenesis relative to wild-type mice.

These results demonstrate that when bgn is absent, the angiogenic response required for a fracture to heal is mitigated. Additionally, bgn expression colocalizes with endostatin expression in regions of bone formation, and bgn is able to inhibit the effect of endostatin in functional assays. This provides a mechanism by which bgn's effect is mediated. Interestingly, next generation sequencing indicates that bgn has a role with integrins in angiogenesis, and it is through inhibition of integrins that endostatin mediates its antiangiogenic effect.
Multiparametric MRI (mpMRI) has improved detection of clinically significant prostate cancer (PCa); however, its capacity to predict oncologic outcomes such as the presence of pathological extraprostatic extension (+pEPE), positive lymph nodes (+pLN) and biochemical recurrence (BCR) is under investigation. Tumor contact length on MRI (TCL), defined as the length of a lesion in contact with the prostatic capsule, is a novel marker with promising early results. We evaluated the ability of mpMRI-determined TCL in predicting +pEPE, +pLN and BCR in patients undergoing robotic-assisted radical prostatectomy (RARP). A review of a prospectively maintained database of men with PCa who underwent prostate mpMRI followed by RARP without prior therapy from 2007-2015 was performed. T2-weighted images were used to measure TCLs of all lesions. Logistic and Cox regression analysis were used to assess associations of clinical, imaging, and histopathological variables with pECE, pLN and BCR. Receiver operating characteristic curve analysis was used to compare predictive ability of TCL to Partin tables. We found that 87/379 (23.0%), 18/384 (4.7%) and 33/371 (8.9%) patients had +pEPE, +pLN and BCR, respectively. Patients with worse pathology and oncologic outcomes had longer median TCL compared to those without these characteristics (+pEPE: 19.8 vs 10.1mm, p<0.0001, +pLN: 38.0 vs 11.7%, p<0.0001 and BCR 19.2 vs 11.2%, p=0.001). On multivariate logistic and Cox regression analysis, TCL was an independent predictor of +pEPE (OR 1.04, 95% CI: 1.02-1.07; p=0.001), +pLN (OR 1.07, 95% CI: 1.03-1.12; p<0.0001) and BCR (HR 1.03, 95% CI: 1.01-1.06; p=0.02). TCL thresholds yielding highest sensitivity and specificity for predicting +pEPE and +pLN were 12.5 mm and 19.7 mm, respectively. The ability of MRI TCL to predict +pEPE and pLN was similar to Partin tables. (pEPE:TCL_{AUC}: 0.66 vs Partin_{AUC}: 0.71, p=0.21; pLN:TCL_{AUC}: 0.77 vs Partin_{AUC}: 0.88, p=0.04). In conclusion, TCL was a good predictor of EPE, pLN and BCR.
2015-2016 Medical Research Scholars Program

Scholar: David Kuo
School: University of California, San Diego, School of Medicine
Mentors: Robert Nussenblatt, M.D., M.P.H., Distinguished NIH Investigator and Chief, Laboratory of Immunology; H. Nida Sen, M.D., M.H.S., Director, Uveitis and Ocular Immunology Fellowship Program
Institute: National Eye Institute (NEI)
Research: Differentiating Endophthalmitis from Uveitis and Lymphoma by Aqueous and Vitreous IL-6 and IL-10 Levels

Endophthalmitis and intraocular lymphoma often masquerade as chronic idiopathic uveitis with nonspecific inflammation, leading to delayed diagnosis and treatment of these vision and life-threatening diseases. Unfortunately, current diagnostic tests remain relatively insensitive. Our branch has shown that intraocular IL-6 and IL-10 levels can differentiate intraocular lymphoma from noninfectious uveitis. However, no published work has investigated the ability of IL-6 and IL-10 to differentiate endophthalmitis from uveitis or lymphoma, which is the goal of this project.

Patients with aqueous or vitreous IL-6 or IL-10 levels and definitive diagnoses of endophthalmitis, uveitis, or intraocular lymphoma were retrospectively included in the study. Intraocular cytokine levels between diagnoses were compared by Kruskal-Wallis and Dunn tests. A gradient-boosted decision tree was trained to classify endophthalmitis vs. uveitis and lymphoma from vitreous IL-6 and IL-10, vitreous IL-6 only, and aqueous IL-6 only data sets. Testing was done by 80-20 train-test split and three-fold cross-validation of the training set.

Seven endophthalmitis, 29 lymphoma, and 49 uveitis patients were included in the study. IL-6 was higher in endophthalmitis than uveitis (p=0.0713 aqueous, 0.0014 vitreous) and lymphoma (p=0.0032 aqueous, 0.0001 vitreous). IL-10 was higher in lymphoma than uveitis (p=0.0017 aqueous, 0.0014 vitreous). Three-fold cross validation demonstrated 95±5%, 95±4%, and 97±5% predictive accuracy for vitreous IL-6 and IL-10, vitreous IL-6 only, and aqueous IL-6 only data sets. Vitreous IL-6 and IL-10 and aqueous IL-6 only data sets achieved 100% predictive accuracy upon validation with the testing set, and the vitreous IL-6 only data set achieved 90% predictive accuracy with 100% sensitivity, 89% specificity and an ROC/AUC of 94%.

Despite limited sample size, machine learning differentiated endophthalmitis from uveitis and lymphoma by IL-6 and IL-10 with high sensitivity and specificity. A larger cohort is needed for further validation.
Psoriasis is a chronic inflammatory skin disease, associated with increased vascular inflammation, accelerated coronary heart disease, and an elevated relative risk of cardiovascular events, beyond traditional risk factors. As such, the disease serves as an ideal clinical human model to study the role of inflammation in atherosclerosis.

Coronary computed tomography angiography (CCTA)-identified low-attenuation, positive remodeling, and/or spotty-calcification, are characteristics of rupture-prone, or “high-risk” coronary plaques (HRP). Numerous studies suggest that HRP are predictive of prospective cardiovascular events. Further research suggests that increased vascular inflammation, as assessed by FDG PET/CT, may be associated with the presence of HRP. As psoriasis patients are known to have increased vascular inflammation, it is reasonable to suspect that they may therefore have an increased prevalence of HRP. To date, however, no study has attempted to characterize HRP morphology in psoriasis patients.

We hypothesized that psoriasis patients would have an elevated prevalence of HRP, as compared to healthy controls. To examine this question, psoriasis patients (N=85), and healthy controls (N=25), underwent CCTA and deep cardiometabolic phenotyping as part of an ongoing cohort study. Though the study groups were of similar baseline age, gender distribution, and had similar Framingham Risk, psoriasis patients had significantly increased non-calcified coronary plaque burden (psoriasis: 1.19 ± 0.46 vs controls 1.09 ± 0.38, p =0.04). Additionally, psoriasis patients were noted to have an elevated prevalence of HRP (psoriasis: 32.9% vs controls 8%, p < 0.001), beyond adjustment for traditional risk factors. Though preliminary, our study lends pathogenic insight to the known increased risk of myocardial infarction seen in psoriasis patients. It additionally may allow for more accurate cardiovascular risk stratification within this vulnerable population.
Much of the weight of decision-making for chronically critically ill patients falls to surrogates. Many studies have focused on the degree to which surrogates reflect the wishes of patients with an underlying assumption that surrogates’ treatment choices ought to accurately reflect patient preferences. Other studies have focused on the burden of the decision-making process such as psychological distress and decisional regret. Yet, this literature has not sufficiently captured the complexity of surrogate decisions for critically ill patients. The purpose of our study was to increase clinician understanding of the perspectives and concerns of surrogate decision-makers as events unfolded in real-time. We conducted a secondary, qualitative analysis of data obtained from the multi-center, randomized-control trial (RCT) entitled “Informing Decisions in Chronic Critical Illness” that determined the effect of family informational and emotional support meetings led by palliative care specialists on family and patient-centered outcomes in chronic critical illness. Of the 365 surrogates who participated in the RCT, 51 surrogates had audio-recorded conversations that underwent qualitative analysis. Through selection and categorization of quotes from transcripts derived from the supportive information team meetings, we recognized four main ways in which surrogates defined their role: (1) voice for the patient, (2) advocate for the patient, (3) advocate for oneself, and (4) advocate for others. Surrogates also use different strategies (i.e. finding balance, exhibiting a sense of perspective, finding strength, knowing what the patient would not want, drawing from previous experiences, acknowledging the burden, sharing the role) in fulfilling their roles. Such factors show that surrogate decision-making does not entirely comport with the standards of substituted judgment. In working through the decision-making process with caregivers, physicians need a more profound understanding to help guide them through the social, emotional, and ethical components that surrogates weigh in when caring for their loved ones.
GATA2 is a transcription factor required for the proliferation and differentiation of hematopoietic stem cells (HSCs) and lymphatic vasculature. Heterozygous mutations in the GATA2 gene result in decreased levels of functional GATA2 protein and cause symptoms due to haploinsufficiency. With the recognition of more cases of GATA2 deficiency and the subsequent screening of additional family members, we have observed phenotypical variability within families with the same mutation. In some families, disease penetrance appears to be complete with most, if not all, known mutation-positive family members exhibiting severe disease symptoms. However, in other families, disease penetrance is reduced, with some mutation-positive family members manifesting severe disease while other mutation-positive members are unaffected or exhibit mild symptoms, at least so far.

The severity of GATA2 disease was classified for 76 GATA2 mutation positive family members in 20 families using a scoring system. We hypothesized that families with regulatory mutations were more likely to contain members without severe manifestations since GATA2 expression levels may vary when the coding sequences remain intact. Indeed, all families with regulatory mutations included mildly affected members compared with only 40% of families with coding mutations (p=0.02). Only families with coding mutations exhibited complete penetrance of severe GATA2 disease. Examining those families with reduced penetrance of severe disease, regulatory mutations were also associated with higher proportions of mildly affected family members than coding mutations were (71% vs. 33%, p<0.001).

It can be hypothesized that coding mutations more commonly result in severe disease due to greater deficiency of functional GATA2 protein levels compared with regulatory mutations. Other changes found in untranslated regions of the GATA2 gene may also affect GATA2 expression. Discovering the specific mechanisms by which some GATA2 mutation positive family members remain largely asymptomatic may allow for alternative directed treatments.
Radiation exposure from computed tomography (CT) is a growing concern, especially given the wide and increased use of CT in recent years. Iterative reconstruction is a method of reducing image noise and thereby enabling scanning at lower tube currents to achieve a lower radiation dose. Here, we focus on next generation model based iterative (mIR) reconstruction and its potential to allow radiation dose reduction while maintaining image quality and diagnostic accuracy.

This prospective IRB-approved study included 100 consecutive patients (60% male, average age, 56.5 +/- 13.1; age range 27-76 years) who underwent a clinically-guided contrast enhanced CT examination of the chest, abdomen and pelvis and a second lower radiation dose research scan. Standard clinical dose CT scans were reconstructed using FBP (STD-FBP), and low radiation dose scans were reconstructed with FBP (LOW-FBP) and mIR (LOW-mIR). Signal intensity and noise measurements were taken from numerous locations in the chest and abdomen.

Image quality for each reconstruction strategy was assessed by two independent readers using six subjective parameters. Data analysis was performed with paired t-test.

The median dose length product for the reduced radiation dose scan was 72% lower than the standard clinical scan (1246.8 vs. 335.8, p<0.001). The CT number measurements for the aorta, muscle and fat in the abdomen were not significantly different between STD-FBP, LOW-FBP and LOW-mIR. LOW-mIR had significantly less image noise than either STD-FBP or LOW-FBP and higher signal-to-noise. Subjectively, STD-FBP did better than LOW-mIR in all six parameters investigated. However, the next step in our study will be to determine whether this preference for STD-FBP translates to changes in diagnostic accuracy across our three reconstruction groups.
The microbiota consist of a diverse array of microbes that localize to various barrier surfaces throughout the body. Our previous work showed that under steady state conditions, the gastrointestinal tract and the skin function in a compartmentalized fashion, where protective immunity in the skin is dependent on the skin microbiota, but not the gut microbiota. However, whether gut microbiota can modulate cutaneous immunity in inflammatory settings has not been addressed. We used mice raised in the absence of live microbes (germ-free) and compared these with mice colonized with bacteria that preferentially colonize the gut. We topically applied imiquimod, which induces IL-17 driven inflammation, to the skin of these mice. Gut bacteria colonized mice had increased skin inflammation compared to germ-free mice (p<0.01). We analyzed the cutaneous T-cell response and found that IL17-producing γδ T-cells, particularly those negative for Vγ4, were driving the increased inflammatory response in gut bacteria colonized compared to germ-free mice. We then characterized the gut-associated γδ T-cells and found an increase in Vγ4+ and Vγ4- IL17 producing γδ T-cells in specific pathogen-free (SPF) compared to germ-free mice (p<0.01 and p=0.04, respectively). We also found increased numbers of Vγ4+ and Vγ4- cells in the peripheral blood of SPF compared to germ-free mice (p<0.01 for both). Furthermore, the IL17 polarization of gut-associated γδ T-cells was correlated with increased ear thickness in the imiquimod inflammatory model (r=0.85, p<0.01). These results suggest that under inflammatory settings, intestinal commensal bacteria may have a profound impact on skin inflammation through the mucosal deployment of circulating γδ T-cells to the skin, findings that could broaden our understanding of the etiology of inflammatory skin disorders.
Phosphaturic mesenchymal tumors (PMTs) are rare FGF23-secreting tumors associated with the paraneoplastic syndrome, tumor-induced osteomalacia (TIO). There is limited information regarding the etiology or cellular origin of PMTs.

**FN1-FGFR1 Translocation in TIO:** A recent report of a novel FN1-FGFR1 gene fusion in a set of PMTs suggests that this translocation and the resultant activation of FGFR1 signaling pathway may be important in PMT tumorigenesis and/or FGF23 production by PMTs. To test the role of the FN1-FGFR1 translocation in PMT tumorigenesis, we performed Fluorescence In Situ Hybridization (FISH) on the NIH collection of PMTs. Of 24 total tumors, 22 have been assessed to date. 45% were FISH positive for the fusion (9/20), 1/20 was deemed intermediately positive for having more positive signals than negative, but did not meet criteria for being fusion positive, 6/20 were fusion negative, and 6/20 were inconclusive. All six inconclusive tumors were from bone, which suggests the typical method used for decalcification, which is known to damage macromolecules, prevented a positive or negative FISH signal.

**Cell/Tissue Origin of PMTs:** The dual observations of: 1) bone-related mesenchymal tissues in PMTs (chondroid matrix, osteoclasts, and bone) and 2) the fact that bone cells are the physiologic source of FGF23, led us to hypothesize that PMTs are transduced from skeletal stem cells. To test this hypothesis, we performed co-localization studies with bone- and tumor-related markers by immunofluorescence and confocal microscopy. Bone markers included alkaline phosphatase (Alk Phos) and RANKL, both mid-stage bone cell lineage markers, and DMP1, a late-stage bone cell lineage marker; tumor-specific markers included FGF23 and GALNT3 (a galactosylaminotransferase responsible for glycosylating FGF23 and protection from enzymatic cleavage). We found that FGF23-secreting tumor cells co-localize with Alk Phos, RANKL, and DMP1. The presence of these bone cell lineage markers provides support for the hypothesis that PMTs arise from transduced skeletal stem cells. There is also co-localization with GALNT3 and FGF23-secreting tumor cells, suggesting PMTs not only produce FGF23, but also express the enzymatic machinery necessary to make intact hormone. Further experiments will focus on cells experimentally transduced with the FN1-FGFR1 chimeric gene to allow for more detailed investigation of this protein and FGFR1 signaling in tumorigenesis and FGF23 regulation.
Previous studies have found associations between one-carbon metabolism nutrients and risk of several cancers, but little is known regarding upper gastrointestinal tract (UGI) cancer. We analyzed pre-diagnostic serum concentrations of several one-carbon metabolism nutrients (vitamin B12, folate, vitamin B6, riboflavin, and homocysteine) in a nested case-control study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study of male Finnish smokers. 127 non-cardia gastric adenocarcinoma (NCGA), 41 esophago-gastric junctional adenocarcinoma (EGJA), and 60 esophageal squamous cell carcinoma (ESCC) incident cases were identified within ATBC. Controls were matched to cases on age, date of serum collection, and follow-up time. One-carbon nutrient concentrations were measured in fasting serum samples collected at baseline (up to 17 years prior to cancer diagnosis). Odds ratios (OR) and 95% confidence intervals (CI)—adjusted for Helicobacter pylori infection, pepsinogen I level, and other confounders—were calculated using conditional logistic regression.

Lower pre-diagnostic vitamin B12 concentrations at baseline were associated with a 5.8-fold increased risk of NCGA (95% CI = 2.7 to 12.6 for lowest compared to highest quartile, p-trend < 0.001). This association remained in participants who developed cancer more than 10 years after blood collection, and after restricting the analysis to participants with clinically normal serum vitamin B12 (>300 pmol/L).

Lower pre-diagnostic vitamin B12 concentrations were associated with an increased NCGA risk. As vitamin B12 absorption requires intact gastric mucosa to produce acid and intrinsic factor, our findings suggest vitamin B12 as a possible biomarker for the atrophic gastritis that precedes NCGA.
Mutations in SLC26A4 are often detected in North American Caucasians with enlarged vestibular aqueduct (EVA), the most common radiologic abnormality in children with sensorineural hearing loss. One-fourth have two mutant alleles ("M2"), one-fourth have one mutant allele ("M1"), and half have no mutant alleles ("M0"). In a cohort of six multiplex families, affected M1 sibling-pairs with EVA were noted to always carry the same "wild type" allele in *trans* to the mutant allele. We hypothesized that the "wild type" allele in M1 patients carries one or more pathogenic sequence variants. Genotype analysis using short tandem repeat markers within and flanking SLC26A4 in the six M1 families was used to identify meiotic recombination breakpoints within each affected sibling pair, which together defined a smallest region of overlap (SRO) of 8.2 Mb on the "wild type" chromosomes 7 in the six families. Massively parallel sequencing (MPS) of the SRO showed that five of six "wild type" chromosomes in M1 individuals shared the same 12 uncommon variants (minor allele frequency ≤0.05 in European control chromosomes in 1000 Genomes), referred to as the "TPK haplotype," in the intronic and intergenic regions upstream to SLC26A4. Haplotypes of additional unrelated M1 EVA individuals were determined by Sanger sequencing. The TPK haplotype was present on seven of nine M1 "wild type" chromosomes and on 31 of 1006 European control chromosomes (2-tailed Fisher’s exact test, p<0.0001). M1 "wild type" chromosomes carry the TPK haplotype at a frequency significantly different from that seen in European control chromosomes. One or more variants of the TPK haplotype may be pathogenic, or the variants in the haplotype may be in linkage disequilibrium with the true pathogenic variant.
In patients with brain tumors, vasogenic edema accumulates in the adjacent brain tissue contributing to significant morbidity and mortality. This type of edema is mediated largely by Vascular Endothelial Growth Factor (VEGF), which disrupts the blood-brain-barrier (BBB) leading to leakage of fluid into the parenchyma. Changes in expression and functionality of tight junction proteins like Claudin-5 are the assumed mechanism of BBB disruption. Clinically, glucocorticoids are typically used in the treatment of vasogenic edema, especially dexamethasone. Despite being the standard of care, however, dexamethasone’s molecular mechanisms of action are poorly understood. We sought to study the underlying molecular mechanisms of glucocorticoid action by employing an \textit{in vivo} model of chronic vasogenic edema treated with systemic dexamethasone.

We surgically placed a cannula into the striatum of the brain in rats and infused vascular endothelial growth factor (VEGF) over 6 days. Select rats were also given systemic dexamethasone via intraperitoneal injections under the same VEGF infusion conditions. Control rats were infused with carrier protein in PBS. Confirmation of edema and BBB breakdown was performed using high-field (9.4T) magnetic resonance imaging on infusion days 2 and 6. Rats were then sacrificed, their brains harvested and used in subsequent molecular studies (immunohistochemistry, immunofluorescence, western blot, qPCR).

Our study demonstrated two important findings. First, chronic VEGF infusion results in upregulation of the tight junction protein Claudin-5 in endothelial cells at the cannula site compared with both the ipsilateral edematous and contralateral non-infused striatum regions. This contradicts \textit{in vitro} studies using VEGF on endothelial cell cultures, but is likely explained by the effect of chronic VEGF infusion in an \textit{in vivo} model. We propose that VEGF induced distortion of endothelial cell morphology disrupts the integrity of the BBB with a compensatory increase in production of non-functional Claudin-5.

Second, we demonstrated that dexamethasone may act through changes in VEGF receptor-2 expression. VEGF-R2 expression on brain endothelial cells typically only occurs during early development and endothelial cell pathology in response to VEGF. Our data confirms endothelial VEGF-R2 expression exclusively near the infusion site in the chronic VEGF rats. Furthermore, systemic treatment with dexamethasone caused marked decrease in VEGF-R2 expression on endothelial cells.
ABCB1 and ABCG2 are ATP-binding cassette (ABC) transporters localized to the plasma membrane where they mediate efflux of xenobiotics, including potential therapeutics in multiple organ systems as well as the blood-brain barrier (BBB). The most common type of brain tumors are metastases to the brain and the mechanisms of BBB bypass have yet to be understood. Additionally, zebrafish have increasingly become a popular model organism due to their rapid maturation, small size, ease of genetic manipulation, initial translucency, and potential for performing high-throughput screens.

We investigated the activity of multiple orthologues of human ABC transporters which have been identified in zebrafish and have shown to be functional on the BBB. We investigated two orthologues of human ABCB1 (ABCB4 and ABCB5) and four orthologues of ABCG2 (ABCG2a-d) in hopes of better understanding the BBB and to increase understanding the nature of species differences between human and zebrafish ABCB1 and ABCG2 function for extrapolations from zebrafish data to be made. We created cell lines individually expressing the six zebrafish orthologues of ABCB1 and ABCG2 and compared their activity to cell lines expressing human ABC1 and ABCG2 for efflux of fluorescent substrates. The fluorescent substrates rhodamine 123, bodipy-verapamil, bodipy-taxol, calcein–AM and the inhibitors dofequidar, cyclosporine A, gefitinib, DCPQ, valspodar, fumitremorgin C (FTC), and elacridar were used to determine efflux function of ABCB1 orthologues. The fluorescent substrates pheophorbide A, bodipy, mitoxantrone and the inhibitors tariquidar, dofequidar, cyclosporine A, and elacridar were used to determine efflux function of ABCG2 orthologues.

Substrate and inhibitor specificity zebrafish were found to be similar to their human counterparts. The overlapping substrate and inhibitor specificity supports interpretation of zebrafish models in understanding the clinical, pharmacological, and physiologic roles of ABCB1 and ABCG2.
2015-2016 Medical Research Scholars Program

Scholar: Akhil Muthigi
School: Wake Forest University School of Medicine
Mentor: Peter A. Pinto, M.D., Head, Prostate Cancer Section; Director, Urologic Oncology Fellowship, Urologic Oncology Branch
Institute: National Cancer Institute (NCI)
Research: Missing the Mark: Prostate Cancer Upgrading by Systematic Biopsy over MRI/TRUS Fusion Biopsy

Multiparametric MRI (mpMRI) and fusion biopsy (FBx) detect more high-risk prostate cancer (PCa) and less low-risk PCa than systematic biopsy (SBx). However, there remains a small subset of patients where SBx captures higher grade disease than FBx. We aimed to identify potential mechanisms for failure of FBx biopsy in detection of clinically significant (CS) PCa.

We reviewed a prospectively maintained database of patients undergoing mpMRI followed by FBx and SBx from 2007-2014. In patients whose disease was upgraded to CS disease (Gleason ≥7) by SBx over FBx, independent re-review of MR imaging, archived biopsy imaging, and whole mount pathology, as well as needle coordinate mapping, were conducted. Multivariate logistic regression analysis was performed to determine predictors for upgrading by SBx.

Disease upgrading based on SBx over FBx occurred in 135/1003 (13.5%) patients, of which only 62 (6.2%) were to intermediate (Gleason=7) [N=51, 5.1%] or high-risk PCa (Gleason ≥8) [N=11, 1.1%]. On multivariate analysis, lower PSA (p <0.001), higher MRI prostate volume (p <0.001), and lower number of target cores (p <0.001) were predictors of upgrading by SBx. Main mechanisms for under-grading by FBx included mpMRI reader oversight, presence of MR invisible cancer, FBx technique error, and intra-lesion Gleason heterogeneity.

MRI and FBx rarely misses CS PCa, as only 62/1003 (6.2%) cases were upgraded to CS disease by SBx. Imaging and biopsy techniques are continually refined and further studies will help to clarify mechanisms of FBx failure and patient populations which benefit from SBx in addition to FBx.
Ovarian cancer is the deadliest gynecologic malignancy, killing over 14,000 women annually. Women are typically diagnosed at an advanced stage. Despite recent advances in cytoreductive surgery and chemotherapy, the majority of women suffer relapse of their disease. As such, there remains a need for novel treatment modalities. Given the heterogeneity of ovarian cancer, it is imperative to identify subtype-directed treatments. The novel antibody NEO-201 is a genetically humanized monoclonal antibody developed through vaccines with tumor-associated antigens (TAAs). This antibody targets malignant tissues that express tumor-specific epitopes in membrane-anchored protein CEACAM-6, providing a tumor-directed approach. This study aimed to identify the cancer subtypes which express the NEO-201 target and demonstrate its cytotoxic effects *in vitro* and in murine models of ovarian cancer.

We performed immunohistochemistry (IHC) on tissue microarrays from ovarian cancer samples to estimate the incidence of cancers expressing the NEO-201 target. In tissue microarrays, NEO-201 demonstrated high reactivity in 12-15% of ovarian samples across two sample sets. Similar expression patterns identified in representative ovarian cancer cell lines by IHC and Western blot directed our choice of *in vitro* models. Using fluorescent cell viability assays, we examined the cytotoxicity of NEO-201 against a high-expressing ovarian cancer cell line *in vitro*. NEO-201 in combination with highly active natural killer (haNK) cells stimulated significant antibody depended cellular cytotoxicity (ADCC) in cell lines expressing its target.

In order to study the effects of immunotherapy in the ovarian cancer murine models, we developed a model using 3D ultrasound to follow cell line tumor xenografts in the mouse ovarian bursa. Calculated tumor volumes from 3D models of the ovarian tumors allow for continual assessment of tumor growth and therapy efficacy prior to ultimate necropsy and metastasis analysis. Studies are ongoing to further investigate NEO-201 cytotoxicity in the ovarian cancer murine models as well as to better identify the mechanism of tumor cell death and the target epitope of NEO-201.
Cancer cells harboring p53 mutations have been shown to exhibit gain of function (GOF) properties including microenvironment effects that are permissive to tumor growth and spread. However, it remains uncertain how these GOF effects are elicited by such mutant p53 isoforms. Current efforts investigate whether GOF properties are elicited through exosomes, particularly in regard to macrophages.

Exosomes are 30-100 nm vesicles shed by all cells that carry bioactive cargo including protein, RNA, DNA, and lipids. Furthermore, exosome uptake has been shown to produce active effects in recipient cells. Exosomes are becoming increasingly implicated in cancer effects on the microenvironment.

Macrophage activation exists on a spectrum, ranging from phagocytic, classically activated M1 macrophages, to M2 macrophages, which exhibit immunosuppressive effects while stimulating vasculogenesis. Our studies have shown that mutant p53 isoforms tilt macrophage phenotype toward M2, possibly enabling tumor growth and metastatic potential.

Mutant p53 was found to be more prevalent in exosomes compared to wild type p53, suggesting possible unique mutant p53 effects through exosomes. However, research continues in order to uncover p53 interactions influencing exosome cargo and release as well as influences on macrophage phenotype.
Hematopoietic stem cell transplantation (HSCT) treats various malignant and non-malignant diseases. Graft-versus-host disease (GVHD) is a common complication of allogeneic-HSCT in which immune cells transplanted from a non-identical donor recognize the transplant recipient as foreign, thereby initiating an immune reaction driven by CD4+ and CD8+ αβ T cells. Organs affected in chronic GVHD (cGVHD) include the skin, GI tract, liver, eyes, mouth, lungs, and joints, often causing significant morbidity, non-relapse mortality, and decreased quality of life. Because available treatments are often ineffective and cause significant side effects, cGVHD continues to be a major hurdle in improving patient outcomes post-transplantation.

Different subsets of donor CD4+ and CD8+ αβ T cells, including T naïve (T n), T central memory (T cm), T effector memory (T em), and T regulatory (T reg) cells, have been shown to have differential functional roles in pre-clinical models of cGVHD. Some subsets appear pathogenic while others have immunoregulatory functions that may ameliorate disease. These T cell populations remain poorly defined within GVHD-affected skin.

Using a mouse model of cGVHD driven by minor antigen mismatch, we sought to identify immune changes in CD4+ and CD8+ T cell subsets in mouse skin at clinically relevant time points post allogeneic-HSCT. We analyzed cell populations via flow cytometry and found that the proportion of T regs relative to all CD4+ T cell subsets decreased, while the proportion of T em cells increased in the allogeneic setting, suggesting that unchecked T em expansion, particularly to the detriment of T reg cells, is a major contributor to development of skin cGVHD.

Future studies will focus on investigating ways to exploit differences between subsets in order to enhance T reg and reduce T em expansion, thereby selectively targeting only the disease-inducing T cell subset for development of more effective, less toxic therapies.
The antidepressant response to a single infusion of subanesthetic-dose ketamine is transient in most depressed patients; however, a minority of patients continue to have an extended response. We examined potential clinical predictors and depressive symptoms in these subjects to better identify such patients a priori. All subjects were treatment-resistant, were experiencing a major depressive episode of at least moderate severity, were unmedicated (major depressive disorder) or on therapeutic-dose lithium or valproate (bipolar depression), and received a single 0.5 mg/kg ketamine infusion. Data were collected pre-infusion (baseline) and on days one, 14, and 28 post-infusion. Twelve of 93 (12.9%) of participants continued to meet response criteria (50% reduction in MADRS score) at two weeks and 4/33 (12.1%) at four weeks. All depressive symptoms were improved at two weeks in responders except for sleep duration/depth. Family history of an alcohol use disorder in a first-degree relative ($r = -.23$, $p = .04$) and dissociation during the infusion ($r = -.29$, $p = .005$) were associated with antidepressant effect at two weeks. Improved apparent sadness, reported sadness, inability to feel, and concentration difficulties at one day correlated most strongly with improvement at two weeks. In conclusion, static (family history of alcohol use disorder) and dynamic (improved sadness, anhedonia, and concentration at one day post-infusion, dissociation during the infusion) factors may have clinical utility in predicting if a patient will have an extended response to ketamine.
Human Immunodeficiency Virus (HIV) affects 36 million people worldwide, with one to two million new infections occurring each year. HIV devastates the immune system by primarily targeting and depleting CD4+ T cells, making patients susceptible to life-threatening infections and malignancies. Current antiretroviral therapy has turned what was once a death sentence into a manageable chronic disease; however, therapy is subject to toxic side effects, lifelong use, and development of viral resistance. Thus, further study of HIV pathogenesis is necessary to identify new therapeutic strategies and targets for eradication of this virus that prominently plagues the human population.

In recent years, novel discovery and characterization of binding between HIV and the T cell surface adhesion molecule α4β7 has established that: HIV has a preference for α4β7 + CD4+ T cells; viral binding to α4β7 enhances viral infectivity; and blockage of α4β7 reduces viral transmission and plasma viral load. Most recently, our lab has found that HIV not only binds α4β7, but it also selectively hijacks α4β7 from host T cells to incorporate α4β7 into the surface of nascent virions.

We aimed to elucidate the mechanism that regulates incorporation of α4β7 into virions to determine why α4β7 is selected for incorporation and the impact of incorporation on viral pathogenesis. We mutated the cytoplasmic domain of α4β7 postulating that inhibition of virion incorporation would confirm which mutated region was necessary for incorporation. Mutant α4β7 constructs and HIV-1 DNA were co-expressed in a 293T cell line to synthesize virions that could potentially exclude incorporation of α4β7. Virions were harvested and assayed for levels of α4β7 incorporation with an α4β7-specific antibody. Unexpectedly, certain mutations in α4β7 actually increased virion incorporation. These mutations bias the activation state and conformation (active/extended >> inactive/bent) adopted by α4β7, so incorporation may be more dependent on α4β7’s conformational state than on the structure of its cytoplasmic domain.
A major cognitive theory on the etiology of attention-deficit hyperactivity disorder (ADHD) arises from observational studies using traditional psychological tests. The classic finding in these tests is the inability of ADHD subjects to maintain a regular rhythm of responses to task stimuli, defined as intraindividual variability (IIV). In this study, we used ex-Gaussian analysis to more accurately assess IIV. Ex-Gaussian analysis incorporates both normal and exponential components. Tau (the mean and standard deviation of the exponential component) examines the reaction times (RTs) causing the IIV. The goal of this study was to use virtual reality (VR) to test this theory because of its ecological validity and its ability to ensure that IIV is not an artifact of head movement.

A head-mounted display was used to place a participant in a 3D virtual classroom that had a task where the participant clicked a button whenever the target letter “X” was presented after the letter “A”. We examined horizontal head movements (yaw) by centering and scaling to Z scores. The parameters of ex-Gaussian (in particular, tau) were found by evaluating the RTs to all the correct responses and within a field of view (FOV) of 0.5 SD.

FOV was associated with only inattention (F(1,95)=2.7, p=0.02). There was a statistically significant positive correlation between the tau for all the correct responses and tau for all the correct responses within a FOV of 0.5 SD (Spearman rho=0.65, p<0.0001; Cronbach’s alpha=0.75; Intraclass Correlation=0.7). Finally, there was no statistically significant association between tau and symptoms of ADHD.

ADHD symptoms are only modestly associated with inability to retain a narrow, focused FOV. Tau is stable when the FOV is considered. Tau is not associated with ADHD, indicating that the IIV is not influenced by participants not looking at the target but most likely from a more organic process.
Chimeric Antigen Receptor (CAR) T-cells are an emerging immunotherapy with successes in both pediatric and adult hematologic malignancies. Currently, toxicities to CAR therapy include “On-Target/Off-Tumor” effects, severe inflammatory cytokine-related toxicities, and persistent pancytopenias. We investigated these toxicities on mature and progenitor hematopoietic subsets using a novel-functional xenograft model of normal human hematopoiesis. We were particularly interested in evaluating this in a CAR T-cell targeting the surface tyrosine kinase receptor Flt3. Flt3 is an attractive target for CAR therapies due to its expression on both AML and ALL as well as its high risk for malignancy when mutated.

Expression of Flt3 on normal progenitor subsets raises the possibility of On-Target/Off-Tumor toxicity. To evaluate this, we utilized immune compromised mice engrafted with human CD34+ stem cells and treated them with matched CAR T-cells directed against various target antigens. While toxicity by a Flt3-CAR T-cell was seen in the CMP, GMP, and MEP subsets, “B-cell restricted” CD19 and CD22-directed CAR induced a similar and more severe reduction in lymphoid progenitor cells. The reduction in these progenitors was reflected in production of mature circulating myeloid cells. Importantly, it thus appears that the hematopoietic stem cell subset is relatively spared. This would indicate that the persistent cytopenias are related to some innate quality of CAR-type adoptive cell transfer rather than a target-specific effect. This is reflected anecdotally by persistent pancytopenias in the CD22 CAR T-cell clinical trial at the NCI and other ongoing CAR trials. There is also evidence from donor leukocyte infusion trials and chronic infection settings that high levels of pro-inflammatory cytokines can dramatically impact bone marrow function. More work is needed to fully characterize the inflammatory cytokine milieu in CAR therapy and its effects on sensitive populations within the bone marrow compartment.
The published literature is indispensable for the interpretation of complex clinical data. For example, while researchers have developed many bioinformatics tools to predict the pathogenicity of specific nucleotide mutations, there is still no substitute to clinical research for genetic interpretation. Unfortunately, the results of such studies are spread throughout the published literature. Broad access to this information has traditionally only been possible through the efforts of teams of human curators who find relevant studies and note them in databases such as UniProtKB or ClinGen. Computational tools have proven useful in curating such databases by processing written text to recognize and normalize mentions of entities such as genes, mutations and diseases. Nevertheless, few systems exist which identify the contextual relationships between such entities, even though the identification of these relationships is essential for database curation.

We proposed a fully automated tool to identify relationships in published literature between genes, mutations and diseases. Our approach utilizes a machine-learning classifier to identify disease-mutation relationships and then accesses global knowledge from outside publications and the Web to identify the correct genes for a given disease-mutation pair. It also incorporates an amino-acid sequence validation step.

Our full approach achieves a precision of 0.82 and recall of 0.77, resulting in a 28% improvement over the F1-measure (from 0.62 to 0.79) of the previous state of the art. We applied our tool to detect all mentions of genetic variants associated with age-related macular degeneration along with ten other diseases in abstracts in PubMed. We then compared our results with two manually curated genotype-phenotype databases. The results of this comparison were consistent with those of the benchmark dataset. In the future, we plan to apply our tool to detect pleiotropic associations in the literature and validate them using clinical genetic data.
Microglia, the primary resident immune cell in the CNS, have been studied in the retina, but predominantly in rodent models that lack a macula. To understand how microglia may demonstrate specialization within the macula and how this specialization may change with aging, we examined the distribution and morphology of microglia at different retinal positions in young and aged primate retina. Flat-mounted foveal, outer macular, and extramacular peripheral retina were isolated from young adult (4.2-5.5 years) and middle-aged (16.8 -18.2 years) female Rhesus macaque primates. Immunohistochemistry for Iba1 (microglia), cone arrestin (cones), and isolectin IB4 (vasculature) was performed and imaged with confocal microscopy. Morphological analysis was performed using ImageJ software.

Microglia in the primate retina vary in density across retinal locations. They demonstrate regional specialization with highest densities found in areas close to the fovea, followed by the outer macula, and lowest densities in the periphery. Around the foveal avascular zone, microglia in the IPL were arranged in a circular pattern with their long axes tangential to the foveal center.

Microglial morphologies vary across retinal locations. OPL foveal microglia show radial elongated morphologies, while those in the macula and periphery lack polarization. OPL macular microglia have more branches, total length of dendrites, and are larger than those in the periphery, possibly relating to a greater synaptic load in the macula. Microglial densities demonstrate changes with aging, increasing in foveal and macular locations but remaining unchanged in the periphery.

Primate retinal microglia demonstrate regional specialization, which may reflect their endogenous functions in synapse maintenance. They increase in density in the aging primate fovea and macula, which may relate to the changing immune environment in the aging macula.
Von Hippel-Lindau (VHL)-associated hemangioblastomas (VHL-HB) arise in the infratentorial central nervous system, and are a leading cause of morbidity and mortality in VHL disease. Surgical resection of symptomatic VHL-HB is effective in managing morbidity from symptomatic VHL-HBs. Surgically unresectable VHL-HBs or those in frail patients are challenging problems. Therapies targeting oncologic and vascular endothelial growth factor (VEGF) pathways have failed to demonstrate tumor control. Our experience, and reports in the literature on VHL-HB avidity to somatostatin analogues, suggested that targeting somatostatin receptor (SSTR) expression might offer an alternative therapeutic strategy. We explored this strategy by demonstrating consistent histologic expression of SSTR1, 2a, 4, and 5 in VHL-HB cells. We found that the somatostatin analogue octreotide induces apoptosis in VHL-HB stromal cells in a dose-dependent fashion by modulation of the BAX-caspase-3 pathway, unrelated to the canonical VHL pathway. When administered to a patient with unresectable symptomatic suprasellar hemangioblastoma, octreotide resulted in tumor volume and symptom stabilization, and tumor cytopenia on repeat Ga-DOTA-TATE positron emission tomography (PET) within 6 months, suggesting tumor infarction. We conclude that VHL-HBs harbor multiple SSTR subtypes that offer actionable chemo-therapeutic strategies for management of symptomatic, unresectable tumors by somatostatin analogue therapy.
Using new and highly successful techniques in deep learning, convolutional neural networks (CNN), and other computer vision techniques, we sought to classify, localize, and segment abdominal organs automatically. A strong motivation in using deep learning was to avoid using image registration-based techniques (i.e. ATLAS) for classification and segmentation, which consists of high computational costs (high-performance computing), hand-crafted features, and limited flexibility of what kind of dataset can be analyzed.

Using a dataset from the Beyond the Cranial-Vault Synapse Challenge, with IRB approval, 50 labeled CT scans from two clinical studies were used to train the CNN. Upon extracting the features from the CNN, additional features from a landmark detection algorithm were incorporated. This allows for a more structured input (spatial locations of the organs in the abdomen) to obtain more precise feature extraction and further minimize over-fitting. Finally, classification was done using a multi-class linear support vector machine (SVM).

Software development was performed on a Linux desktop, with a Nvidia Titan Z GPU (for deep learning). The deep learning framework utilized was Keras/Theano. Promising results were obtained. While the CNN performs most of the heavy lifting, the addition of spatial features extracted from the landmark detection algorithm further improved results, and also resulted in reducing potential over-fitting (reduced over-fitting on pixel intensity). A SVM approach to classification was utilized over the standard Softmax classification in CNN, which also slightly improved results.
Bombsin-like receptor 3 (Brs3) is an orphan G-protein coupled receptor expressed in the brain and in beta cells of the pancreas. Deletion of the Brs3 gene in mice leads to a late onset obesity phenotype with reduced sympathetic tone and increased food intake. On the other hand, Brs3 agonism drives increases in body temperature and decreases in food intake and body weight. In the brain, Brs3 is expressed in several hypothalamic nuclei, including the dorsomedial hypothalamus (DMH) and the paraventricular nucleus of the hypothalamus (PVH). We found that micro-infusion of the Brs3 agonist MK 5046 into the DMH of anesthetized mice raised BAT temperature while similar infusions into PVH did not. In order to assess the effects of activation of Brs3 neurons in freely moving mice, we utilized chemogenetics. We selectively expressed Designer Receptors Exclusively Activated by Designer Drugs (DREADD) hM3D(q) in Brs3-T2A-CreERT2 mice in the DMH or the PVH. Chemogenetic activation of DMHBrs3 neurons yielded increases in body temperature while chemogenetic activation of PVHBrs3 neurons only minimally increased body temperature. However, chemogenetic activation of PVHBrs3 neurons decreased food intake by 40% while DMHBrs3 activation did not affect food intake. Physical activity was not affected by chemogenetic activation of either Brs3 population. These results reaffirm that Brs3 neurons are involved in energy homeostasis. More importantly, we have identified that the effects of Brs3 agonism, increased body temperature and decreased food intake, are mediated by different loci.
Metastatic melanoma has a 5-year survival rate less than 20% with standard chemotherapy, with a median overall survival of 6-10 months. Recently, immune checkpoint inhibitor ipilimumab (CTLA-4 mAb) was FDA approved for metastatic melanoma. Melanoma has a heterogeneous response to ipilimumab; however, a subset of patients have a very durable response, approaching ten years since the early clinical trials, leading to a common goal of increasing the number of patients who respond to treatment.

Previously, our lab developed a mouse melanoma model that exhibited a heterogeneous response to CTLA-4 mAb, and we utilized this model to explore enhancing melanoma response to CTLA-4 mAb. In animal studies, immunogenic tumors have been associated with a better response to CTLA-4 mAb, and in human melanomas melanocyte differentiation proteins (tyrosinase, TRP2, GP100) have been reported to act as antigens when overexpressed. Prior studies in our lab identified that dopadecarboxylase (DDC) inhibitors, such as carbidopa and benserazide, potentially increase expression of melanocyte proteins, and we postulated that DDC inhibitors might thereby enhance CTLA-4 mAb response. We demonstrated that carbidopa increases tyrosinase protein level \textit{in vitro} and mRNA level \textit{in vivo} in A375P in human melanoma cells. We then tested combination carbidopa and CTLA-4 mAb in immunocompetent mice with syngeneic melanoma. Carbidopa treatment alone slowed aggressive melanoma growth.

Mice receiving combination therapy also experienced less aggressive tumor growth compared to CTLA-4 mAb alone during dosing. However, after carbidopa dosing concluded, tumors in the mice receiving carbidopa alone grew comparable to control groups. Similarly, tumor growth in the combination therapy group became comparable to mice treated with CTLA-4 mAb alone, resulting in no significant difference in survival between the two groups. In conclusion, we showed DDC inhibitors do increase expression of a “differentiation antigen” tyrosinase in melanoma cells. Carbidopa alone has an effect in slowing mouse melanoma tumor growth, and may be beneficial for enhanced CTLA-4 mAb response if dosed continuously due to its temporal effect. Finally, further studies will investigate whether DDC inhibitors increase immunogenicity of mouse melanoma or act through a different and/or additional mechanism.
Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries. However, the pathogenesis of the disease remains unknown. Calcium has been found within drusen, retinal deposits that are characteristic of AMD. The purpose of this study was to evaluate calcium intake as a risk factor for development and progression of AMD. Our goal was to investigate whether increased calcium intake was associated with a higher risk for AMD development and progression in AREDS participants.

We retrospectively analyzed Age-Related Eye Disease Study (AREDS) participants (n=4751) for the association of calcium intake and progression to intermediate AMD (large drusen) or late AMD (neovascularization or geographic atrophy (GA)), between 1992 and 2005. We estimated calcium intake (dietary and supplementary) based on responses to a baseline dietary questionnaire. Baseline and annual fundus photographs were graded at a reading center using a standardized protocol to assess the progression of AMD. We conducted analyses using Cox regression models with the Wei-Lin-Weissfield technique and adjusted for age, gender, race, educational attainment, BMI, smoking history, anti-inflammatory drug usage, and AREDS treatment group.

The participants in the highest quintile of dietary calcium intake had a lower risk of developing AMD than those in the lowest quintile: late AMD (HR: 0.73, 95% CI: 0.59, 0.90), central GA (HR: 0.65, 95% CI: 0.48, 0.88), and neovascular AMD (HR: 0.78, 95% CI, 0.61, 1.00). The participants in the highest tertile of supplementary calcium intake had a lower risk of developing neovascular AMD (HR: 0.68 95 % CI: 0.48, 0.95) when compared with those who did not take calcium supplements.

In the AREDS participant population, higher levels of dietary and supplementary calcium intake were associated with a lower incidence of progression to late AMD. The strengths of our study include its longitudinal nature and the large cohort of participants with AMD.
Innate lymphoid cells (ILCs) comprise a recently identified category of immune cells that derive from a common lymphoid progenitor. While they are similar to T-cells in both phenotype and effector function, ILCs mature in the bone marrow and lack specific antigen receptors. Group 2 innate lymphoid cells (ILC2s), in particular, are important mediators of type 2 immune responses and, thus, have been found to contribute to allergic inflammation.

ILC2s have been associated with atopic dermatitis, but the exact contribution of this ILC subgroup to skin immunity, as well as their phenotypic description in the skin, is still unclear. Therefore, the objective of our study was to characterize ILC2s in the different layers of the skin during homeostasis and atopic inflammation in a mouse model.

Flow cytometry analyses of established markers revealed that ILC2s in the epidermis, dermis, and subcutaneous tissue expressed distinct phenotypic markers. Furthermore, skin ILC2s exhibited distinct cytokine- and chemokine-dependency for development. These findings indicate that skin ILC2s appear to be more heterogeneous than previously appreciated and suggest that their phenotypes may be shaped by microenvironmental factors. In addition, topical application of MC903, a vitamin D3 analog, on mouse trunk skin resulted in macroscopic and histologic features that recapitulated atopic dermatitis and were accompanied by an increased abundance and activation of skin ILC2s. This mouse model may be used to study the role of ILC2s in initiating and/or driving atopic inflammation. In summary, our findings contribute to a deeper understanding of skin ILC2s and their role in skin immune regulation.
Introduction: Ionizing radiation (IR) is commonly used to treat thoracic malignancies. Exposure of adjacent normal lung may result in lung injury and fibrosis. Recently, we reported that accelerated senescence of type II pneumocytes results in parenchymal depletion and precedes pulmonary fibrosis. Arachidonate 12-lipoxygenase (12-LOX) oxidizes arachidonic acid to form 12-hydroxyeicosatetraenoic acid (12-HETE), a pro-inflammatory mediator. We hypothesized that mice deficient in ALOX-12 would be resistant to IR induced senescence and fibrosis.

Methods: C57/Bl6j (WT) and Alox12 homozygous knockout (Alox12-KO) mice (n>3 per group) were exposed to thoracic IR (0Gy, 5Gy, 17.5Gy, 5x5Gy, or 6x5Gy). Fibrotic foci were identified with aniline blue staining of fixed lung sections. 12-LOX mRNA and protein were assessed in WT lungs after IR with microarray, quantitative PCR, and western blotting. In vitro studies with primary murine pneumocyte cultures and A549 cells included staining for senescence associated β-galactosidase activity and western blotting for NOX4, p21, and PML following IR and 12-HETE treatment.

Results: A significant increase in 12-LOX mRNA and protein was observed in murine lungs exposed to fibrogenic doses of IR (17.5 Gy, 5x5 Gy and 5x6 Gy) compared to low dose IR (5 Gy) or controls (0 Gy). 12-LOX deficiency significantly reduced fibrotic foci in murine lungs receiving fibrogenic doses of thoracic IR (6x5 Gy) at 18 weeks. Treatment of murine primary pneumocytes with 12-HETE (1 and 150 nM) increased pneumocyte senescence 2.1-fold. Treatment of primary murine pneumocytes with 12-HETE increased the expression of senescence markers NOX4, p21, and PML, paralleling increases observed after IR. Similarly, human type II pneumocyte A549 cells exhibited increased 12-LOX expression in β-galactosidase-stained senescent cells at 3 days after IR.

Conclusion: 12-LOX is a critical mediator of radiation lung fibrosis and type II pneumocyte senescence. 12-LOX may serve as a novel therapeutic target for mitigating IR-induced lung fibrosis.
Heat shock proteins Hsp40, Hsp70 and Hsp90 are molecular chaperones required for stabilization/activation of nuclear receptors, including full-length androgen receptor (AR) and glucocorticoid receptor (GR). Although ligand-binding domain (LBD) targeted (LBDT) therapy initially inhibits AR function, thereby improving patient survival, this treatment invariably leads to emergence of castration-resistant prostate cancer (CRPC). CRPC is frequently characterized by elevated expression of alternative nuclear receptors able to at least partially maintain the AR transcriptional program. These nuclear receptors include GR and a number of constitutively active AR splice variants lacking the LBD (ARv). While full length GR and AR depend on the Hsp40/Hsp70/Hsp90 chaperone axis for activity, the chaperone requirements of ARv are not known. Because Hsp90 interacts with the LBD, ARv are insensitive to Hsp90 inhibitors. However, we believed that ARv, like GR and AR, retain dependence on Hsp40/Hsp70. After applying for and being awarded a Department of Defense Innovation Grant ($750,000, 3 years) we began a collaborative approach (intramural with Developmental Therapeutics; extramural with UCSF) to begin testing this hypothesis. We used combined biophysical, genetic, biochemical and pharmacological approaches, including novel small molecules able to bind and inhibit both Hsp40 and Hsp70, to begin a synergistic group of studies. These studies have started laying the foundation for a detailed and comprehensive picture of the specific chaperone dependence of these individual nuclear receptors in cells and tumor xenografts. The preliminary stages of in vivo xenograft data and ex vivo evaluation of patient tumor biopsy tissue have provided early proof-of-principle confirmation that inhibition of Hsp40 and Hsp70 represents a novel strategy to target the continued nuclear receptor dependence of CRPC. As we accumulate additional in vitro and in vivo models, we will test whether this targeting strategy also can abrogate or delay onset of resistance in LBDT therapy-naïve patients.
A digital and quantitative assessment of scleritis activity can facilitate patient care and establish reproducible, masked measures for clinical research. This is important for facilitating collaborative efforts and increasing statistical power when studying a rare disease.

We performed a clinical validation study of an image-based standardized grading system of scleritis by evaluating the agreement between graders using clinical exam grades versus digital photo grades. We also evaluated the intra-rater reliability of digital gradings.

Eight scleritis patients were evaluated prospectively over a total of 95 visits as part of a clinical trial. A score of 0 to 3+ was assigned to each quadrant of the study eye by using photographic guidance (NEI scleritis grading system). Clinical grading based on exam was unmasked and was performed by two investigators. Digital gradings based on slit lamp photos collected at each visit were determined by using a standardized screen. There were a total of 115 photos. Two independent graders were masked to the order of the images, which was randomized. Intra-rater reliability was evaluated by repeated grading on a random sample of 20 photos.

Reliability analysis demonstrated moderate agreement between clinical and digital gradings (weighted kappa coefficient $\kappa = 0.60$). Bland-Altman analysis showed that digital grades disagreed by +0.43 steps higher than clinical grades (95% limits of agreement, -0.88 to 1.74). Intra-rater reliability of the digital grading was very good ($\kappa = 0.89$).

Digital grading using a standardized grading scale for scleritis based on digital slit lamp photos is a reliable method of quantifying inflammatory activity, and it has the potential to allow use of reading centers for scleritis trials. However, the difference between clinical and digital gradings should be recognized and accounted for. The next step would be to investigate how clinical and digital grades correlate to overall scleritis clinical course.
Obesity and metabolic syndrome have emerged as a pandemic health crisis over the past several decades, driven largely by increases in intake of energy-dense foods high in fat and sugar and a concomitant decrease in physical activity. Given the limited number and effectiveness of therapies that achieve long-lasting weight loss, there is an acute need for novel appetite-suppressing drugs. To inform and guide the design of such drugs, it is critical to understand the neural circuitry that regulates food intake.

We focused in our studies on the lateral septum, a brain region known to mediate both feeding behavior and responses to hedonic rewards like drugs and food, and neurons expressing glucagon-like peptide receptor 1 (GLP1R), a hormone known to regulate food intake. Using a mouse model and optogenetic techniques involving cre-dependent viruses that delivered the cation channelrhodopsin specifically to septal GLP1R-expressing neurons, we were able to probe the circuitry of these cells.

We first demonstrated that the activity of GLP1R-expressing neurons in the lateral septum responds to nutritional state. In mice fasted overnight, activity of septal GLP1R neurons was decreased relative to that of animals that were fasted overnight and then refed. Using an optogenetic approach, we then showed that activation of these septal GLP1R neurons decreases food intake. Finally, we were able to map out the multiple projection targets of septal GLP1R neurons using both placental alkaline phosphatase staining and a fluorescently tagged channelrhodopsin selectively delivered to these neurons. Notably, a number of these downstream projection fields are known to be involved in feeding behavior, such as the lateral hypothalamus, the periaqueductal gray, and the ventral tegmental area. In summary, our studies describe a previously unreported role for septal GLP1R neurons in regulating feeding behavior.
Index

Clinical Center (CC)

Comfort O. Elumogo
Case Western Reserve University School of Medicine
David A. Bluemke, M.D., Ph.D., Ms.B., FAHA, FACP, Director, Radiology and Imaging Sciences; Senior Investigator, National Institute of Biomedical Imaging and Bioengineering

Lingsheng Li
University of Oklahoma College of Medicine
Marion Danis, M.D., Head, Section on Ethics & Health Policy, Department of Bioethics; Ann Berger, M.D., Chief, Pain and Palliative Care Services

Andrew M. Sohn
Sidney Kimmel Medical College at Thomas Jefferson University
Ronald M. Summers, M.D., Ph.D., Senior Investigator; Chief, Clinical Image Processing Service; Chief, Imaging Biomarkers and Computer-Aided Diagnosis (CAD) Laboratory

National Cancer Institute (NCI)

Taylor J. Aiken
Cleveland Clinic Lerner College of Medicine of Case Western University
Udo Rudloff, M.D., Ph.D., Gastrointestinal Oncology Section, Thoracic and Gastrointestinal Oncology Branch

Nicole A. Colwell
Florida International University Herbert Wertheim College of Medicine
Mark R. Gilbert, M.D., Chief, Neuro-Oncology Branch

Matthew D. Greer
Cleveland Clinic Lerner College of Medicine of Case Western University
Peter Choyke, M.D., Director, Molecular Imaging Program, Center for Cancer Research

Michael Kongnyuy
University of South Florida Morsani College of Medicine
Peter Pinto, M.D. Head, Prostate Cancer Section, Urologic Oncology Branch

Christian M. Mustroph
Emory University School of Medicine
Michael Gottesman, M.D., Chief, Laboratory of Cell Biology; Head, Multidrug Resistance Section, NCI; Deputy Director for Intramural Research

Akhil Muthigi
Wake Forest University School of Medicine
Peter A. Pinto, M.D., Head, Prostate Cancer Section; Director, Urologic Oncology Fellowship, Urologic Oncology Branch

Monica K. Neuman
Creighton University School of Medicine
Christina Annunziata, M.D., Ph.D., Principal Investigator, Women’s Malignancies Branch

James S. Nix
University of Arkansas for Medical Sciences College of Medicine
Curtis C. Harris, M.D., Chief, Laboratory of Human Carcinogenesis

Brittany U. Oliver
George Washington University School of Medicine & Health Sciences
Ronald Gress, M.D., Chief, Experimental Transplantation and Immunology Branch; Head, Transplantation Immunology Branch; Deputy Director, Center for Cancer Research; and Nataliya Buxbaum, M.D., Assistant Clinical Investigator, Experimental Transplantation and Immunology Branch

Christopher T. Sauter
Emory University School of Medicine
Terry Fry, M.D., Head, Hematologic Malignancies Section, Pediatric Oncology Branch

Renee M. Thomas, Ph.D.
David Geffen School of Medicine at UCLA
Glenn Merlino, Ph.D., Co-Chief, Laboratory of Cancer Biology and Genetics; Acting Scientific Director for Basic Research

Amanda Truong
University of Utah School of Medicine
Keisuke Nagao, M.D., Ph.D., Earl Stadtman Investigator, Dermatology Branch

Luca F. Valle
Geisel School of Medicine at Dartmouth
Deborah Citrin, M.D., Senior Investigator, Radiation Oncology Branch

Matthew J. Watson
Michigan State University College of Osteopathic Medicine
Leonard M. Neckers, Ph.D., Head, Tumor Cell Biology Section, Urological Oncology Branch

National Cancer Institute-Division of Cancer Epidemiology and Genetics (NCI-DCEG)

Eugenia H. Miranti
Northwestern University Feinberg School of Medicine
Gwen Murphy, Ph.D., M.P.H., Staff Scientist, Metabolic Epidemiology Branch; Christian Abnet, Ph.D., M.P.H., Chief, Metabolic Epidemiology Branch

National Center for Biotechnology Information (NCBI)

Michael A. Simmons
University of Arizona College of Medicine
Zhiyong Lu, Ph.D., Stadtman Investigator, Biomedical Text Mining Group, NCBI; Emily Chew, M.D., Deputy Clinical Director, NEI; Deputy Director, Division of Epidemiology and Clinical Applications, NEI
David Kuo
University of California, San Diego, School of Medicine
Robert Nussenblatt, M.D., M.P.H., Distinguished NIH Investigator and
Chief, Laboratory of Immunology; H. Nida Sen, M.D., M.H.S., Director,
Uveitis and Ocular Immunology Fellowship Program

Michael A. Simmons
University of Arizona College of Medicine
Zhiyong Lu, Ph.D., Stadtman Investigator, Biomedical Text Mining
Group, NCBI; Emily Chew, M.D., Deputy Clinical Director, NEI; Deputy
Director, Division of Epidemiology and Clinical Applications, NEI

Janani Singaravelu
Ohio State University College of Medicine
Wai T. Wong, M.D., Ph.D., Chief, Unit on Neuron-Glia Interactions in
Retinal Disease

Alanna K. Tisdale, M.D.
Warren Alpert Medical School of Brown University
Emily Chew, M.D., Deputy Director, Division of Epidemiology and
Clinical Applications; Deputy Clinical Director, NEI

Maggie M. Wei
Georgetown University School of Medicine
H. Nida Sen, M.D., MHSc, Director, Uveitis and Ocular Immunology
Fellowship Program

National Heart, Lung, and Blood Institute (NHLBI)

Tsion M. Aberra
Yale University School of Medicine
Nehal Mehta, M.D., M.S.C.E., F.A.H.A.; Lasker Clinical Research
Scholar; Section of Inflammation and Cardiometabolic Diseases

Ishan Asokan
Vanderbilt University School of Medicine
André Larochelle, M.D., Ph.D., Investigator, Regenerative Therapies
for Inherited Blood Disorders, Hematology Branch

Lauren G. Banaszak
Cleveland Clinic Lerner College of Medicine of Case Western
University
Neal S. Young, M.D., Chief, Hematology Branch

Elizabeth J. Carstens
University of Texas Southwestern Medical School at Dallas
Adrian Wiestner, M.D., Ph.D., Senior Investigator, Laboratory of
Lymphoid Malignancies

Roop K. Dutta
Warren Alpert Medical School of Brown University
André Larochelle, M.D., Ph.D., Investigator, Hematology Branch

Comfort O. Elumogo
Case Western Reserve University School of Medicine
David A. Bluemke, M.D., Ph.D., Ms.B., FAHA, FACP, Director, Radiology
and Imaging Sciences; Senior Investigator, National Institute of
Biomedical Imaging and Bioengineering

Joseph B. Lerman
Icahn School of Medicine at Mount Sinai
Nehal Mehta, M.D., MSCE, Lasker Clinical Research Scholar, Section of
Inflammation and Cardiometabolic Diseases

Diana P. Melo
New York University School of Medicine
Marcus Y Chen, M.D., Investigator, Advanced Cardiovascular Imaging
Lab, Cardiovascular and Pulmonary Branch

National Human Genome Research Institute (NHGRI)

Barrington A. Quarrie
Wake Forest University School of Medicine
Philip Shaw, B.M.B.Ch., Ph.D., Head, Neurobehavioral Clinical
Research Section, Social and Behavioral Research Branch

National Institute of Allergy and Infectious Diseases (NIAID)

Ehren K. Dancy
Emory University School of Medicine
Christa Zerbe, M.D., M.S., Medical Director, Clinical Services,
Laboratory of Clinical Infectious Diseases; Assistant Program Director,
Infectious Disease Fellowship

Jana P. Lovell
Johns Hopkins University School of Medicine
Steven Holland, M.D., Chief, Laboratory of Clinical Infectious
Diseases; Director, Division of Intramural Research

Eric D. Merrill
University of Missouri - Kansas City School of Medicine
Yasmine Belkaid, Ph.D., Chief, Mucosal Immunology Section

Damilola D. Phillips
Cleveland Clinic Lerner College of Medicine of Case Western
University
Paolo Lusso, M.D., Ph.D., Chief, Viral Pathogenesis Section,
Laboratory of Immunoregulation

Eunice Kennedy Shriver National Institute of Child
Health and Human Development (NICHD)

Lauren A. Barber
Harvard Medical School
Joan Marini, M.D., Ph.D., Senior Investigator and Chief, Bone and
Extracellular Matrix Branch

Ruth J. Davis
Cleveland Clinic Lerner College of Medicine of Case Western
University
Clint Allen, M.D., Principal Investigator, Translational Tumor
Immunology Program; and Carter Van Waes, M.D., Ph.D., Clinical
Director, Head and Neck Surgery Branch; Chief, Tumor Biology Section

National Institute on Deafness and Other
Communication Disorders (NIDCD)

Lauren A. Barber
Harvard Medical School
Joan Marini, M.D., Ph.D., Senior Investigator and Chief, Bone and
Extracellular Matrix Branch

Ruth J. Davis
Cleveland Clinic Lerner College of Medicine of Case Western
University
Clint Allen, M.D., Principal Investigator, Translational Tumor
Immunology Program; and Carter Van Waes, M.D., Ph.D., Clinical
Director, Head and Neck Surgery Branch; Chief, Tumor Biology Section
Adeeb Derakhshan  
Cleveland Clinic Lerner College of Medicine of Case Western University  
Carter Van Waes, M.D., Ph.D., Clinical Director; Chief, Head and Neck Surgery Branch; Chief, Tumor Biology Section

Carter Van Waes, M.D., Ph.D., Clinical Director; Chief, Head and Neck Surgery Branch; Chief, Tumor Biology Section

Tina Munjal  
Johns Hopkins University School of Medicine  
Andrew Griffith, M.D., Ph.D., Scientific Director, NIDCD; Chief, Otolaryngology Branch; Chief, Molecular Biology and Genetics Section

Nina Quintero  
Johns Hopkins University School of Medicine  
Andrew Griffith, M.D., Ph.D., Scientific Director, NIDCD; Chief, Otolaryngology Branch; Chief, Molecular Biology and Genetics Section

National Institute of Dental and Craniofacial Research (NIDCR)

David J. Kirby  
Johns Hopkins University School of Medicine  
Marian F. Young, Ph.D., Senior Investigator, Chief, Molecular Biology of Bones and Teeth Section, Craniofacial and Skeletal Diseases Branch

Tarek Metwally  
University of Michigan School of Dentistry  
Michael Collins, M.D., Chief, Section on Skeletal Disorders and Mineral Homeostasis, Craniofacial and Skeletal Diseases Branch

National Institute of Dental and Craniofacial Research (NIDCR)

Brandon K. Tan  
University of Cincinnati College of Medicine  
Marc Reitman, M.D., Ph.D., Chief, Diabetes, Endocrinology, and Obesity Section

Stephen Xue  
Louisiana State University School of Medicine in New Orleans  
Michael Krashes, Ph.D., Acting Chief, Section on Motivational Processes Underlying Appetite, Diabetes, Endocrinology, and Obesity Branch

National Institute of Mental Health (NIMH)

Chinedu I. Anyaeji  
Cleveland Clinic Lerner College of Medicine of Case Western University  
Alex Martin, Ph.D., Chief, Section on Cognitive Neuropsychology, Laboratory of Brain and Cognition

Steven J. Pennybaker  
Johns Hopkins University School of Medicine  
Carlos Zarate, M.D., Chief, Experimental Therapeutics and Pathophysiology Branch

National Institute of Neurological Disorders and Stroke (NINDS)

Roger B. Murayi  
Perelman School of Medicine at the University of Pennsylvania  
Prashant Chittiboina, M.D., M.P.H., Assistant Clinical Investigator, Surgical Neurology Branch

Saman Sizdahkhani  
Chicago Medical School at Rosalind Franklin University  
Prashant Chittiboina, M.D., M.P.H., Assistant Clinical Investigator, Surgical Neurology Branch
About The Foundation for the National Institutes of Health

The Foundation for the National Institutes of Health (FNIH) procures funding and manages alliances with public and private institutions in support of the mission of the NIH. The FNIH works with its partners to accelerate biomedical research and strategies to fight against diseases in the United States and across the world. The FNIH organizes and administers research projects; supports education and training of new researchers; organizes educational events and symposia; and administers a series of funds supporting a wide range of health issues. Established by Congress in 1996, the FNIH is a not-for-profit 501(c)(3) charitable organization. For additional information about the FNIH, please visit www.fnih.org.

Since 2012, FNIH has raised more than $3.7 million for MRSP. Major donors include:

Alexandria Real Estate Equities, Inc.
American Association for Dental Research
Buffy Cafritz
Colgate-Palmolive Company
Doris Duke Charitable Foundation
Genentech, Inc.
The Leona M. and Harry B. Helmsley Charitable Trust
Howard Hughes Medical Institute
Joel S. Marcus
Newport Foundation, Inc.
Pfizer Inc.